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THE INFLUENCE OF NUTRITIONAL AND HORMONAL FACTORS UPON IMMUNE AND ALLERGIC RESPONSES TO INFECTION*

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THE NATURAL HISTORY of bacterial infection can be divided into a short early stage of invasion and toxæmia associated with destruction of tissue, and a long delayed stage of immunity and repair. The early acute stage causes adrenocortical stimulation resulting in catabolism of body protein; the latter delayed stage is characterized by anabolism of protein associated with an increased production of insulin. The development of immunity to the infection is the turning point, converting the first into the second stage; it ends toxæmia, halts damage and begins convalescence. It also causes a change in the ratio of activity of different endocrine glands. The purpose of this paper is to consider the nature of these changes and how they influence, and are influenced by, the immunological behaviour of the host.

NON-SPECIFIC CONSEQUENCES OF BACTERIAL INFECTION

"Stress"

Selye (1937) showed that "stress" induces in the rat a state of endocrinological imbalance which he includes under the term "adaptation syndrome". In this species, "stress" induces adrenocortical stimulation associated with inhibition or atrophy of the other endocrine glands. The observation is important. But Selye's attempts to apply this finding to man are based on a weak analogy (Long, 1954b, 1955a), the

deficiencies of which will be considered as this article proceeds.

Bacterial damage

In addition to "stress", there are other non-specific consequences of bacterial infection which may, by influencing the metabolism of the host, modify the immunological response to bacterial infection. If diphtheria toxin is injected intradermally into guinea-pigs in doses sufficient to kill half of them (LD 50), a large area of necrosis and inflammation remains in the survivors; these animals fail to gain weight and over a period of months many die. Prompt excision of the inflamed area reduces the mortality and shortens convalescence. These deaths are not directly due to the toxin, but secondary to the presence of a large area of autolysing tissue. Thus specific leads to non-specific damage.

Bacterial allergy and protein metabolism

Bacterial allergens (i.e. tuberculin), like bacterial toxins, are also capable of producing indirect non-specific trauma. It has been shown in my laboratory that, in guinea-pigs, the intradermal injection of tuberculin will, after a delay of a few days, precipitate symptoms of acute protein deficiency in animals in which the condition has previously been subclinical. One of the early symptoms of this deficiency is hypergammaglobulinaemia. Surgery, the injection of pyrogens or simple antigenic stimulation have no such effect. It may be that hypersensitivity to bacterial allergens in general induces a strain on protein metabolism.

In any acute infection, the basal metabolic rate is increased. The supply of substances that the body cannot readily store—water-soluble vitamins (e.g. ascorbic acid) and essential amino acids—may fail. Bergel (1952) suggests that under such conditions, lack of co-enzymes, due possibly to a deficiency of phosphate donors, could upset normal pathways of metabolism.

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Nutritional and hormonal factors may influence immune or allergic responses to infection either because they are present from the onset of the disease or because they are the consequence of infection. Endocrine imbalance or nutritional deficiency may be a non-specific sequel to "bacterial stress". It is unlikely that, under natural conditions, the production of antibody in itself either causes serious nutritional deficiency or is seriously impaired because such a deficiency already exists. Indeed, the addition of biologically valuable food supplements (i.e. egg or milk) to the diet of animals depresses antibody synthesis, whereas a deficiency of protein tends to increase it (unpublished observations). In this connection, it is noteworthy that protein deficiency is usually associated with a compensatory hyperglobulinaemia.

To summarize, the development of immunity ends the acute early stage of bacterial damage; it therefore ends "bacterial stress" (other than that produced by bacterial allergens) associated with adrenocortical hyperactivity and catabolism, and initiates the stage of repair associated with anabolism. Non-specific consequences of bacterial infection produce hormonal and nutritional changes which may in themselves influence the response of the host to infection.

SPECIFIC CONSEQUENCES OF BACTERIAL INFECTION

The specific immune response

Bacterial infection stimulates the formation of fixed (intracellular) antibody, resulting in bacterial allergy, and of circulating (extracellular) antibody, associated with immunity. Some immunologists prefer to make a distinction between circulating antibody (antibacterial immunity) and circulating antitoxin (antitoxic immunity). Such a division has value, for it emphasizes the fact that bacterial antigens are either soluble or insoluble. Soluble antigens include bacterial toxins; they do not require phagocytosis; they are first-rate antigens giving rise to antitoxins. Insoluble antigens include most of the components of the bacterial cell; they require phagocytosis, possibly to bring them into solution in order that they may stimulate antibody formation. They are relatively poor antigens.

It is important to appreciate that bacterial allergy of the tuberculin type is a "normal"

response to bacterial infection; the "normal" person responds to infection with tubercle bacilli by becoming sensitive to tuberculin. In direct contrast, food, drug or pollen sensitivities provide examples of "abnormal" allergic responses. In addition, bacterial allergy of the tuberculin type is a "natural" as opposed to a "laboratory" phenomenon (cf. anaphylaxis and Arthus responses). The isosensitization and autosensitization techniques, so popular at present, are technical modifications of the latter response; their theoretical application to the study of human disease is subject to the general criticisms that apply to the use, for such purposes, of immediate allergic responses (Long, 1954b), and, in addition, the particular criticisms inherent in their modification (Long, 1955b).

There is one other important general point. Antibody is not a single substance with constant properties. A single antigen (i.e. diphtheria toxoid) injected into a single animal (i.e. the guinea-pig) stimulates the production of antitoxin which undergoes quantitative and qualitative change with the stage of immunization. The evidence for this statement is as follows.

The primary and secondary response

Glenny (1931) and his colleagues have shown that a single injection of diphtheria toxoid produces after approximately one month a low level of circulating antitoxin measured in terms of 1/1,000 or 1/10,000 of a unit (the primary response). Once this stage has been reached, a second injection of the antigen causes an immediate copious outflow of antitoxin (the secondary response). Cells must be conditioned by antigen before they can produce antitoxin in quantity (Fig. 1).

Chromatographic analysis

Porter (1955) has shown, by means of chromatography, that rabbit antibody differs with the stage of immunization.

Electrophoretic analysis

Kekwick and his colleagues (Kekwick and Record, 1940; Kekwick *et al.*, 1941) have shown, by means of electrophoresis, that diphtheria antitoxin is present in beta and gamma components of globulin, the proportion of the latter increasing as the stage of immunization lengthens.

Avidity

Kraus introduced the term "avidity" to differentiate quick-acting from slow-acting antitoxin. Glenny and Barr (1932) provided the modern definition of the term as firmness of union between antigen and antibody; they developed an assay method based on ease of separation by dilution of the two.

METHODS

The choice of antigen

Diphtheria toxoid was chosen as the antigen. It stimulates all cells irrespective of their ability to phagocytose. It gives rise to a single type of antitoxin (cf. tetanus toxoid). All the test reagents—diphtheria antigen, antitoxin and toxin—can be standardized so that accumulated ex-

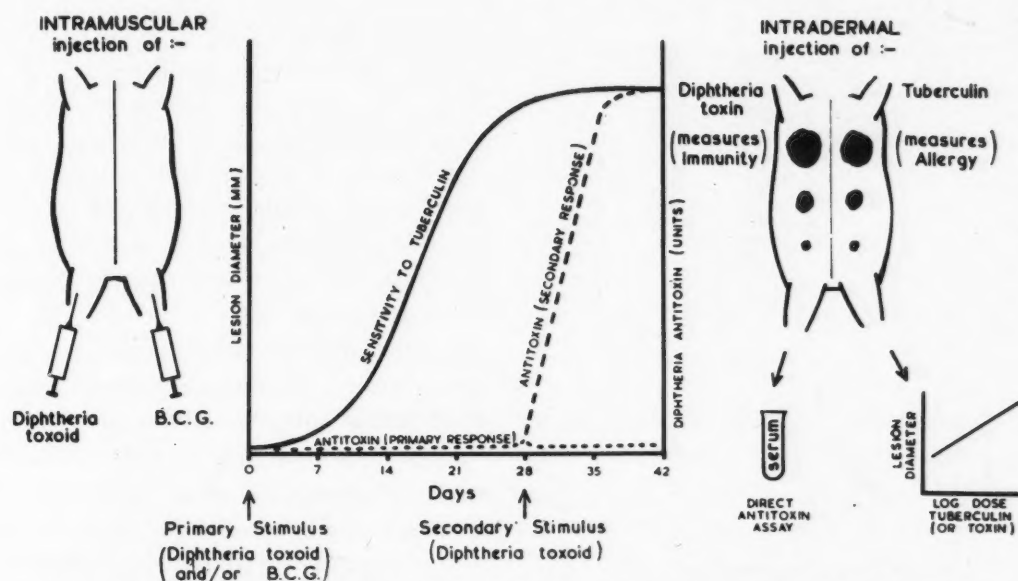


Fig. 1.—Methods for inducing and measuring immune and allergic responses in guinea-pigs.

If a state of competition for toxin is postulated between the tissues on the one hand and the antitoxin on the other hand, avid will protect more than non-avid antitoxin. Unit for unit, avid is more effective than non-avid antitoxin in protecting guinea-pigs against death from diphtheria toxæmia. This argument and experiment lead to the conclusion that "good" antitoxin is avid and "bad" antitoxin is non-avid. However, certain species—the guinea-pig, monkey, and man—tend to produce non-avid antitoxin. Yet children sometimes recover naturally from diphtheria. Moreover, the success of the British prophylactic immunization program is attributed to the presence in the serum of "protected" children of about a ten-thousandth of a unit per ml. of non-avid antitoxin.

Nutritional or hormonal factors, present from the onset of the disease or secondary to bacterial infection, could affect the quantitative or qualitative formation of a fixed or of circulating antibody, the union of antigen with such antibody or the consequences of their union. With these observations in mind, the following experiments were planned.

experience is brought to each new experiment. Diphtheria toxin has the advantage that it causes generalized damage (cf. botulinum toxin), so that the diameter of the lesion resulting from the intradermal injection of the toxin provides a measure of the immunity of the animal (see Miles, 1949; Long, 1950), and also that the effects of delayed non-specific damage, due to autolysis of dead tissue, can be studied. In addition, diphtheria antigens readily induce primary and secondary responses so that the influence of nutritional or hormonal factors on different stages of immunity can be easily analysed. The conditioning of cells and the rate of production of antitoxin are likely to be of greater importance to the welfare of the animal than the final titre, which usually grossly exceeds requirements. Clearly it is essential to select an antigen-antibody system and a technique capable of demonstrating such effects.

The primary stimulus both conditions cells to respond to further antigenic stimulation and causes traces of antitoxin to circulate in the serum. It is important to know whether these two effects run parallel or divergent courses;

whether indeed the latter provides a measure of the former. In addition, if an antigen is going to fail, does it fail to condition cells or to stimulate cells once they have been conditioned? Which is the greater test of the antigen, to produce a primary or a secondary stimulus?

A simple method of analysing the immune response of guinea-pigs to diphtheria toxoid has been devised (Fig. 2). The antigenic stimuli con-

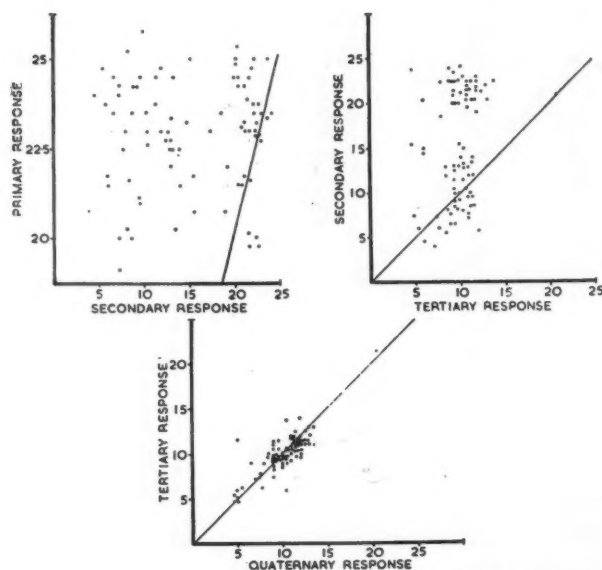


Fig. 2.—Method for analyzing the stages of antitoxic immunity in guinea-pigs.

sist of repeated small doses of standard antigen. The immune response is measured by the intradermal injection of constant doses of toxin, using a modified multiple Schick technique devised by Miles and myself (Long, 1950). The mean lesion diameters resulting from the intradermal injection of constant doses of diphtheria toxin into immune animals are shown in these graphs. When the primary is plotted against the secondary response, the non-immune guinea-pigs are shown in the top right quarter of the graph. Animals that produced little or no primary response, but a marked secondary response, are shown in the top left quarter. In the bottom right quarter are those that produced a good primary, but poor secondary, response. In the bottom left corner are those that produced both a good primary and secondary response. As immunity is measured throughout by the response to a constant dose of a standard toxin, the level of immunity at different stages of antigenic stimulation can be compared. A study of these graphs leads to the following conclusions:

1. The primary response judged by antitoxic immunity is no indication of later immunological behaviour.

2. Primary conditioning of cells is independent of circulating antitoxin. Secondary responsiveness is the only reliable indication of primary conditioning.

3. Primary and secondary responses both vary in degree.

4. Secondary responses tend to be large and depend on primary conditioning of the cells. They may occur in animals in which primary conditioning has been induced without the appearance of circulating antitoxin. There is, therefore, a quantal element (all or none) to the immune response. This is clearly shown in the graph in which the secondary is plotted against the tertiary response.

5. Animals that fail to produce a primary response may produce an equivalent response after further antigenic stimulation.

6. Each animal has its own individual maximum response to this particular antigenic stimulation. This is shown when the tertiary is plotted against the quaternary response.

It is uneconomic to carry out this prolonged immunological procedure in all experiments. The influence upon immunity of each nutritional or hormonal factor has been studied up to the time of, and including, the secondary response. The evidence given represents therefore only a limited stage in the course of a complex and changing immunological mechanism. The main effects obtained are, at present, being subjected to this more detailed method of analysis.

The measurement of fixed antibody (Fig. 1)

Guinea-pigs were sensitized with B.C.G. or with dead tubercle bacilli. There is no evidence of a primary or secondary response in the development of fixed antibody. Sensitivity to tuberculin develops gradually (Fig. 1): whether there is any qualitative change is uncertain. There is no satisfactory method for direct assay of fixed antibody. Traditionally, it is measured indirectly by comparing the size and intensity of lesions resulting from the injection of tuberculin. The method has its limitations, for the degree of sensitivity is influenced by the interactions of a variety of hormonal and nutritional factors; it can change from hour to hour.

The choice of experimental animal

Simple rules of logic must be observed if experimental work is to have the best chance of elucidating human disease. In any argument by analogy, the more ways in which two things are known to resemble each other, the more likely it is that they will resemble each other in ways that are unknown (see Jevons, 1931). In this particular argument it is important to choose an animal that resembles man in response to antigenic stimulation, in being readily sensitized to bacterial allergens, in nutritional requirements, in response to hormones and in endocrinological behaviour in response to "bacterial stress". The guinea-pig responds to antigenic stimulation like man; it is readily sensitized to bacterial allergens like man; it is noteworthy that it shares with man inability to synthesize ascorbic acid and, incidentally, requires similar members of the vitamin B complex. Since the two species have these features in common, the chances are increased that their endocrinological behaviour following "stress" and their response to injected hormones are similar.

Cortisone toxicity for different species

Cortisone is the obvious choice of hormone with which to begin to test these hypotheses, both because the acute early stage of bacterial infection, or indeed "stress" from any cause, induces adrenocortical stimulation, and also because the therapeutic effects of cortisone suggest that the effect of the hormone upon immune and allergic responses to infection deserves study.

Cortisone acetate (50 mg./kg. per day for ten days), injected intramuscularly, caused marked loss of weight in the mouse, rat, rabbit and ferret, but not in the guinea-pig or monkey (Fig. 3). In addition, gamma globulin peaks and antitoxin synthesis were depressed in the mouse, rat, rabbit and ferret, but unaffected in the guinea-pig and monkey. The addition of excess protein in the form of skimmed milk to the diet of rabbits did not prevent this effect (Lloyd and Long, 1954; Long, 1954b). The analogy between man and guinea-pig is therefore maintained (Table I). The rhesus monkey also resembles the latter species in these respects.

This species difference is clear-cut; it has been shown by simple means, is independent of complex argument, and cannot be seriously disputed. It is important, not only because it repre-

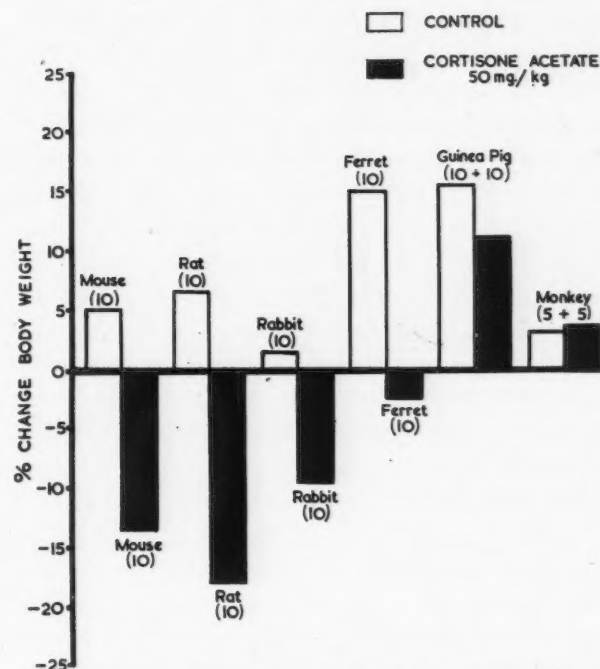


Fig. 3.—Cortisone toxicity for different species.

sents a remarkable stability of a few species to massive doses of cortisone, but also because these species show marked stability in the activity of the thyroid and adrenal glands in response to "stress". The latter fact has wide implications. The guinea-pig, rhesus monkey and man do not develop the "adaptation syndrome" in response to stress. The assumption that they do seriously delayed the progress of this work. Miles and I (1950) showed that cortisone depressed and thyroxine increased sensitivity to tuberculin, and that 14 days later there was a swing in sensitivity in the other direction. The increase in hypersensitivity that occurred 14 days after cortisone treatment had stopped was attributed to a hypothetical compensatory response on the part of the thyroid. Such a state occurs in the rat and the rabbit. Cortisone treat-

TABLE I.

COMPARISON OF SPECIES			
Species	Tuberculin sensitivity	Ascorbic acid synthesis	Response to cortisone
Man Monkey G.-pig	Readily induced	Ascorbic acid not synthesized	Resistant (antitoxin synthesis not depressed)
Rat Mouse Rabbit Ferret	Not readily induced	Ascorbic acid synthesized	Sensitive (antitoxin synthesis markedly* depressed)

*Antitoxin effect not known for ferret.

ment or "stress" (Selye, 1937) depresses thyroid activity (see, for example, Harris, 1955). This phase is succeeded in these species by a phase of thyroid hyperactivity. However, Gross, Pitt-Rivers and I, and later Grey and I (unpublished data), carried out exhaustive experiments with radioactive iodine in attempts to prove that such a state occurred in the guinea-pig, as postulated by Miles and myself (1950). We showed that desensitization with large doses of cortisone and the compensating swing in sensitivity when the drug is withheld, are not, in this species, associated with any demonstrable change in thyroid activity.

My experience of rhesus monkeys is limited to a histological study of the thyroid gland of five rhesus monkeys treated with cortisone acetate (50 mg./kg. per day for 10 days); no difference between the glands of these and the control animals could be detected. Comparable treatment induces marked depression of thyroid activity in cortisone-sensitive species (rat, mouse, rabbit and ferret) with associated histological change. In brief, cortisone-resistant species (Table I) show a greater stability in the activity of the thyroid gland in response to "stress" or to treatment with cortisone than do cortisone-sensitive species. Recently Engstrom and Markardt (1955) have shown that this statement applies to man.

A study of the analogy (Table I) raises an important problem that recurs throughout and remains unsolved. What is the role of the ascorbic acid metabolism in relation to these immunological and hormonal problems? On the immunological side, mild deficiency of ascorbic acid impairs antitoxin production in the guinea-pig (Long, 1950), and the metabolism of ascorbic acid is intimately concerned with the response of the hypersensitive guinea-pig skin to tuberculin (Long *et al.*, 1951c). On the endocrinological side, the activity of the various glands is closely related to ascorbic acid metabolism (Meiklejohn, 1953; Lloyd and Sinclair, 1953).

Lately, Cornforth and I (unpublished) have shown that cortisone-sensitive species (Table I) have a lower concentration of non-protein-SH in the carcass than cortisone-resistant species, and that cortisone induces a significant decrease in this concentration in cortisone-sensitive, but not in resistant, species. Sulphydryl metabolism may provide the link between hormonal balance on

the one hand and ascorbic acid metabolism on the other (Long, 1955b).

HORMONES AND ANTITOXIC IMMUNITY

The adrenal cortex

Adrenocortical stimulation could influence the development of antitoxic immunity in two main ways. It could influence the conditioning of the cells to produce antibody (the primary response) or it could influence the copious outflow of antibody that follows antigenic stimulation of conditioned cells (the secondary response). The action of the adrenal cortex on the latter was considered some years ago by Dougherty and White (1947). Their conclusions, though based on slight evidence, were attractive and received wide attention. Indeed, on general grounds, it was decided to test their hypothesis, which is summarized in Fig. 4. In brief, adrenocortical

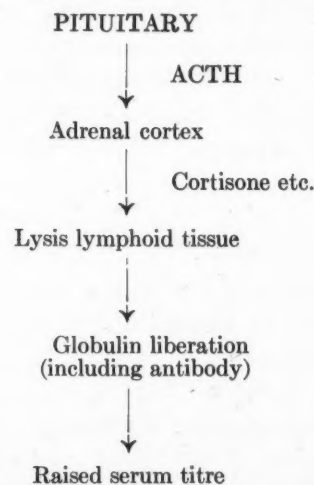


Fig. 4.—Hypothesis of Dougherty and White (1947).

stimulation resulted in an increased output of cortisone and related compounds, which induced lympholysis with liberation of gamma globulin including antibody (Dougherty and White, 1947). Immunological and electrophoretic examination of sera of many different species, at every stage of the immune response to soluble or insoluble antigens, failed to show liberation or increased titre of antibody or antitoxin. These investigations proved, however, that there is a profound species difference in the effect of cortisone upon antibody response. Antibody formation is depressed by cortisone in rats, mice and rabbits (Long and Shewell, unpublished). But, as already stated, the guinea-pig provides a better analogy with man. Work on many hundreds of guinea-pigs with a wide range of antigens showed that in this species the adrenal

cortex has no significant effect on any stage of antibody formation (Long, unpublished).

The thyroid gland

Treatment with thyroxine increases the secondary response of guinea-pigs to diphtheria toxoid. The effect is increased when treatment is prolonged and the dose sufficient to allow animals in the active stage of growth just to gain weight, the aim being to produce con-

The islets of Langerhans

Shewell and I (1955) studied the alternative relationship, namely, that between the thyroid gland and the pancreas. Partial pancreatectomy prevented the action of thyroxine in increasing immunity. Thyroxine induces compensatory hypertrophy of the islets of Langerhans. It is therefore probable that increased immunity in guinea-pigs is due to an increased production of insulin.

TABLE II.

EFFECT OF B.C.G. VACCINE ON ANTITOXIC IMMUNITY IN GUINEA-PIGS

Treatment	Average responses (mean lesion diam.)		Variance ratio* (treatment: animals)	P	Potency ratio	Deaths
D.T.....	19.15	24.05	—	—	1.000	8/15
D.T. + T.T.....	18.58	23.78	< 1	—	0.827 (1.2 fold)	8/15
D.T. + Hyal.....	18.13	23.10	< 1	—	0.632 (1.6 fold)	8/15
D.T./B.C.G. + D.T.....	18.42	23.83	< 1	—	0.809 (1.2 fold)	11/15
B.C.G. + D.T./B.C.G. + D.T...	17.05	21.32	3.07	0.05-0.10	0.297 (3.4 fold)	6/15
B.C.G. + D.T./D.T.....	15.37	20.02	8.72	0.001-0.01	0.152 (6.6 fold)	4/15

*Variance ratio tested with (1,28) df. D.T. = Diphtheria toxoid.
T.T. = Tetanus toxoid. Primary/secondary stimulus.

ditions that stimulate, without overwhelming, compensatory endocrinological hypertrophy. An association was noted between a high level of circulating antitoxin and hypertrophy of both the adrenal cortex and the islets of Langerhans. Thyrotoxicosis is associated in man with lymphoid hyperplasia, and as already stated the hypothesis of Dougherty and White (1947) was current at the time of these experiments. These ideas were combined in a single hypothesis that, under the influence of the thyroid and adrenocortical hormones together, there was a high rate of lymphoid hyperplasia and dissolution with an increased rate of liberation of antibody. A series of experiments destroyed every link in the chain of this complex hypothesis. They proved that thyroxine-induced hyperimmunity was not mediated through the adrenal cortex; that cortisone or corticotrophin had no significant effect on antibody production in either thyrotoxic or non-thyrotoxic guinea-pigs. Not only was there no electrophoretic or immunological evidence of quantitative or qualitative change in circulating antibody, but in addition the ability of circulating antibody to neutralize toxin in the skin of passively immunized animals was unaffected by treatment with cortisone or corticotrophin (Long, unpublished).

THE RELATIONSHIP OF BACTERIAL ALLERGY TO ANTITOXIC IMMUNITY

Specific effects

The hæmolytic streptococcus (for example) produces exotoxins and allergens; therefore, the primary antigenic stimulus and sensitizing process are concurrent; cells are conditioned to produce, at the same time, circulating and fixed antibody. Further liberation of antigen, and of allergen, means that antigenic stimulation (the secondary stimulus) and the hypersensitive response to the allergen occur together. It is important to know whether the hypersensitive state influences antitoxin production and, if so, whether such change can be decreased by desensitizing hormones and increased by hormones that increase sensitivity to bacterial allergens (see below). There is at least a theoretical possibility that hormones might influence, by such indirect means, the development of antitoxic immunity. Opinion is divided between those who consider that hypersensitivity localizes the area of bacterial inflammation (and therefore, presumably, the area of antigenic stimulation) and those who consider that it spreads it (and presumably antigen with it).

Experiments were carried out in guinea-pigs to study the influence of bacterial allergy upon

the development of antitoxic immunity (Table II). In the left-hand column are listed the types of treatment. In group 1, diphtheria toxoid provided primary and secondary stimulation; in group 2, a mixture of diphtheria and tetanus toxoid provided primary and secondary stimulation (the purpose being to see whether the addition of a second simple antigen enhanced the response to diphtheria toxoid).

In group 3, diphtheria toxoid mixed with hyaluronidase provided primary and secondary stimuli (the purpose being to see whether spreading the antigen influenced the antitoxin response). In group 4, the primary stimulus was induced by diphtheria toxoid and the secondary stimulus by diphtheria toxoid mixed with B.C.G. vaccine. In group 5, diphtheria toxoid mixed with B.C.G. was used for both primary and secondary stimuli. With group 6, diphtheria toxoid mixed with B.C.G. was used for the primary, and diphtheria toxoid alone for the secondary stimulus. Immunity was measured by the modified multiple Schick technique (Miles, 1949; Long, 1950; Fig. 1). B.C.G., mixed with diphtheria toxoid to induce a primary stimulus increased immunity significantly; this enhanced effect was slightly (but not significantly) impaired when the secondary stimulus was also combined with B.C.G. B.C.G. did not significantly affect immunity if given to non-sensitized animals with the secondary stimulus. The addition of hyaluronidase or of tetanus toxoid did not significantly influence the immune response.

The ability of tubercle bacilli to enhance immune responses is well known and indeed led to the introduction of Freund's adjuvant. It is probably true to say that anything that increases the local concentration of mononuclear cells increases the antibody response to an antigen. These experiments show that a hypersensitive reaction neither so localized nor so diluted and washed away the antigen that the secondary stimulus failed. Apparently hypersensitivity does not readily impair the concurrent development of antitoxic immunity. It is probable therefore that the influence of hormones upon hypersensitivity will not indirectly influence antitoxin formation to any significant extent.

Non-specific effects

There is another aspect of the problem which has interested me. As already stated, the tuberculin response precipitates symptoms of acute

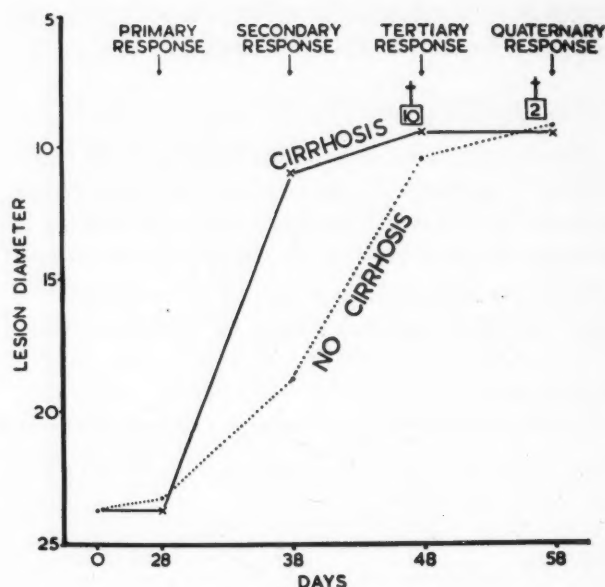


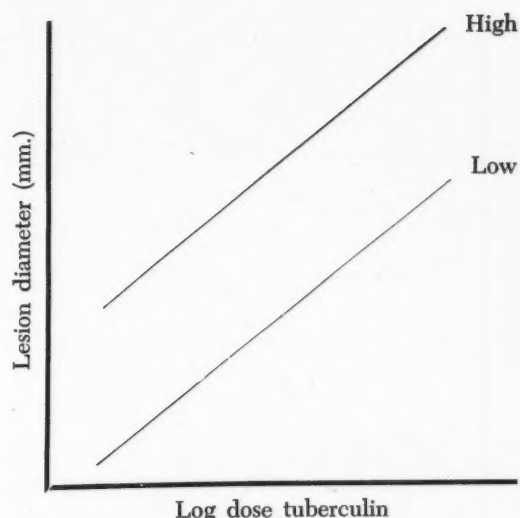
Fig. 5.—Effect of cirrhosis of the liver (secondary to protein deficiency) on antitoxic immunity in guinea-pigs. Numbers in squares denote deaths.

protein deficiency in chronically protein deficient guinea-pigs; it is more effective in this respect than the injection of pyrogens, than simple antigenic stimulation or surgery. A marked increase in gamma globulin and a fall in plasma albumin were associated in the most severely ill animals with cirrhosis of the liver. These animals produced remarkably high titres of circulating antitoxin. Severely damaged animals (with cirrhosis) reached a maximum immune response more quickly than less severely damaged animals (without cirrhosis) but this hyperimmunity was associated with a high mortality from non-specific causes (Fig. 5). The rate of gamma globulin turnover is enhanced with cirrhosis of the liver (see *Nutrition Reviews*, 1953), which may account for the fact that the peak of antitoxin synthesis was reached quickly. This experiment shows clearly how misleading can be generalizations made on a single comparison of titre, timed, for instance, at the secondary response.

HORMONES AND SENSITIVITY TO TUBERCULIN (BACTERIAL ALLERGY)

The adrenal cortex

Miles and I (1950) showed that cortisone acetate depressed sensitivity to tuberculin in guinea-pigs. This effect is specific for the cortisone-hydrocortisone molecule (Long and Spensley, 1954). Corticotrophin causes a decrease in adrenal ascorbic acid; many have postulated



Treatment	Tuberculin sensitivity
Basic diet only.....	High
+ Cortisone.....	High
+ Ascorbic.....	Low
+ Ascorbic + Cortisone.....	Low
+ Cabbage.....	High
+ Cabbage + Ascorbic.....	High
+ Cabbage + Cortisone.....	Low
+ Cabbage + Ascorbic + Cortisone.....	Low

Fig. 6.—Interactions of cabbage, ascorbic acid and cortisone on tuberculin sensitivity in guinea-pigs.

that the vitamin is used up in the synthesis of adrenal steroids. The interrelationships of corticotrophin, of cortisone and of ascorbic acid were therefore studied, using factorial experiments, in the tuberculin-sensitive guinea-pig. Instead of the finding that corticotrophin was less effective than cortisone in ascorbic acid deficient animals, neither hormone had any effect on sensitivity. These unexpected results led to the experiment shown in Fig. 6. The basic diet was deficient only in ascorbic acid. Cortisone was ineffective in ascorbic acid deficient animals. Ascorbic acid depressed sensitivity and this effect was not influenced by cortisone. But ascorbic acid provided in cabbage had no such effect and prevented desensitization by additional ascorbic acid. However, cortisone depressed sensitivity in cabbage-fed animals; the effect must therefore be due to something in cabbage which is lacking in the basic diet. Presumably, this substance is ascorbic acid which induces desensitization in cabbage-fed, cortisone-treated animals. Additional ascorbic acid did not enhance the effect.

Further experiments showed that dehydroascorbic acid, the first oxidation product of ascorbic acid, depressed sensitivity to tuberculin, either in the presence or absence of cabbage. This suggested that in the guinea-pig something

derived from cabbage prevented oxidation of ascorbic acid to dehydroascorbic acid; cortisone antagonized the "cabbage factor". Under natural conditions in the growing leaf, —SH compounds, present in cabbage, maintain ascorbic acid in the reduced state. The hypothesis advanced was that the cabbage factor was such a compound active in the animal. This was supported by the fact that, in the guinea-pig, reduced glutathione behaved like the cabbage factor; alloxan, which does not produce diabetes in guinea-pigs (or, incidentally, in rhesus monkeys) and which combines with —SH compounds, influenced sensitivity to tuberculin in a manner indistinguishable from that of cortisone (Long *et al.*, 1951a, c). (The analogy between species-sensitivity to, and desensitizing action of cortisone and alloxan is important [Table I]. Neither cortisone nor alloxan directly influences sensitivity. These effects are mediated via ascorbic acid [Long *et al.*, 1951c].)

Further experiments showed that skimmed milk or methionine behaved like the cabbage factor. Cabbage is rich in methionine. The cabbage factor is antagonized by ethionine—the anti-metabolite for methionine (Long, 1954a). Recently, the basic diet used in these experiments was shown to contain suboptimal quantities of methionine, thus confirming what had already been postulated (Long, 1954a). There is little doubt that the cabbage factor is methionine. Methionine is a precursor of glutathione and the hypothesis was modified accordingly (Fig. 7).

On the basis of this and of other indirect evidence (Long, 1955a), Cornforth and I (unpublished) postulated that cortisone induces a fall in non-protein-SH in the carcass but not in the viscera, and that it will be more marked in cortisone-sensitive than in resistant species. Direct experiments showed this to be true. But large doses of cortisone acetate were needed to produce small effects. The hypothesis that corti-

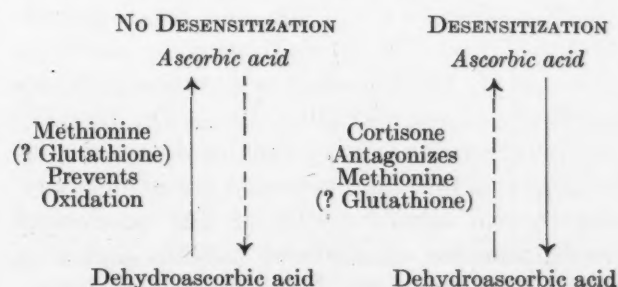


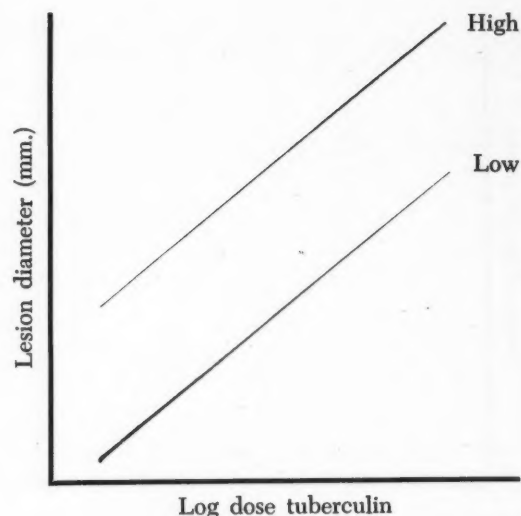
Fig. 7.—Hypothetical explanation of the desensitizing action of cortisone (stage 2).

sone by decreasing the $-SH$ content of the carcass initiates a chain of metabolic events, resulting in a decrease in sensitivity to tuberculin, might be just tenable if the argument was based on experiments carried out in cortisone-sensitive species such as the rat. But it is untrue for the guinea-pig and the rhesus monkey, and therefore probably untrue for man. It may be that cortisone influences $-SH$ groups concerned with activation of a particular enzyme system and that any local change cannot readily be measured by the crude sampling techniques employed by us. Nevertheless, the indirect evidence that cortisone influences $-SH$ metabolism is strong (Long, 1955a). It is possible that improved methods of study will yield direct evidence of such a relationship.

The thyroid gland

Although thyroxine increases sensitivity to tuberculin (Long and Miles, 1950), cortisone depresses sensitivity to the same final level in both thyroxine-treated and control animals (Long *et al.*, 1951b). Propylthiouracil decreases the output of thyroxine and might therefore be expected to decrease sensitivity to tuberculin. This, in fact, did not prove to be the case: propylthiouracil itself had no effect on sensitivity but it prevented the desensitizing action of cortisone. However, a small replacement dose of thyroxine, which in itself had no effect on sensitivity, restored the desensitizing action of cortisone (Long *et al.*, 1951b, Fig. 8).

No further progress was made until Professor Houssay drew my attention to the analogy between his work on the relationship of the thyroid gland to experimental diabetes and that of my colleagues and myself on the relationship of the gland to sensitivity to tuberculin. Since then, his lead has been followed (Long, 1954a, 1955a; Long and Shewell, 1954, 1955). Diabetogenic agents tend to decrease, and anti-diabetogenic agents to increase, sensitivity to tuberculin (Long, 1954a, b). On the one hand, propylthiouracil prevents desensitization by cortisone (Long *et al.*, 1951b), whereas thyroxine increases sensitivity (Long and Miles, 1950). On the other hand, thiouracil reduces the incidence of diabetes in rats subjected to partial pancreatectomy, and thyroid administration at first accelerates the appearance of diabetes mellitus and then cures it by inducing hyperplasia and hypertrophy of the islets (Houssay *et al.*, 1946). There-



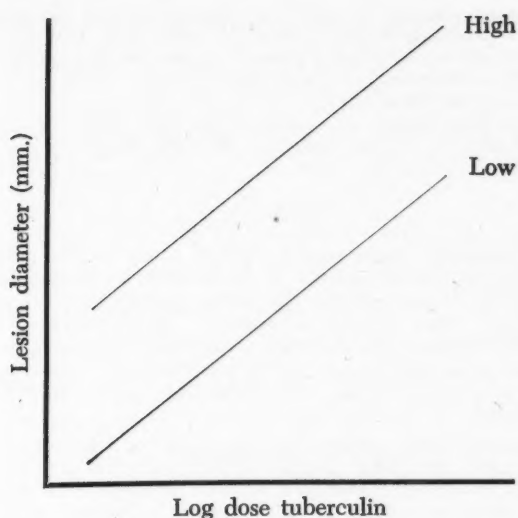
Treatment	Tuberculin sensitivity
Basic diet and cabbage	
+ Cortisone	Low
+ Propylthiouracil	High
+ Thyroxine	High
+ Cortisone + Propylthiouracil	High
+ Thyroxine + Propylthiouracil	High
+ Thyroxine + Cortisone	Low
+ Propylthiouracil	Low

Fig. 8.—Interactions of cortisone, propylthiouracil and thyroxine on tuberculin sensitivity in guinea-pigs. (Small maintenance dose of thyroxine.)

fore, hypo- or hyper-thyroidism opposes the experimental production of diabetes or desensitization. Houssay (1950) attributes the anti-diabetic effect of hypothyroidism to an increase in the free $-SH$ groups of the tissue and that of hyperthyroidism to an increase in islet tissue associated with hyperinsulinism (Houssay *et al.*, 1946). (Recently, Butterfield [1955] showed that disturbances in carbohydrate metabolism, associated in man with adrenocortical hyperactivity or with diabetes mellitus, can be prevented by the $-SH$ compound dimercaprol [BAL].)

In keeping with the Houssay hypothesis, thyroxine increases sensitivity to tuberculin in guinea-pigs via the pancreas; the effect is abolished by partial pancreatectomy and restored with insulin (Long and Shewell, 1954) (Fig. 9). Both hypothyroidism and insulin increase the content of free $-SH$ groups of tissue (Houssay, 1950). It may be that this free $-SH$ opposes both desensitization and experimental diabetes.

It is noteworthy that a study of the influence upon sensitivity of both the adrenal cortex and the thyroid gland should have led to the conclusion that both mediate their effects via $-SH$ metabolism.



Treatment	Tuberculin sensitivity
Nil.....	Low
Thyroxine.....	High
Insulin.....	High
Pancreatectomy*.....	Low
Thyroxine + Pancreatectomy*.....	Low
Insulin + Pancreatectomy*.....	High
Thyroxine + Insulin.....	High
Thyroxine + Insulin + Pancreatectomy*.....	High

* Partial

Fig. 9.—Interactions of insulin, thyroxine and partial pancreatectomy on tuberculin sensitivity in guinea-pigs. (Large dose of thyroxine inducing mild thyrotoxicosis.)

The islets of Langerhans

Insulin increases sensitivity to tuberculin in guinea-pigs (Cornforth and Long, 1954; Long and Shewell, 1954). A simple cross-over experiment showed that insulin hypoglycaemia is associated with marked sensitivity to tuberculin; as the blood sugar rises (due to adrenocortical hyperactivity), sensitivity to tuberculin falls. The level of sensitivity to tuberculin can, therefore, alter in a few minutes as the relative activity of the islets of Langerhans and of the adrenal cortex change (Cornforth and Long, 1953). These two endocrine glands are almost certainly directly concerned with sensitivity to tuberculin; their relative activities are influenced by the thyroid gland and the gonads. The action of the hormones of the latter glands upon sensitivity is indirect.

Growth (diabetogenic) hormone

From what has been said, it is obvious that the influence of the diabetogenic hormone upon sensitivity is likely to be important. But reports of the biological activity of pituitary hormones must be treated with caution. Almost invariably such preparations contain more than one hor-

mone; frequently they are toxic; in addition, biological properties possessed in high degree by one batch of hormone are sometimes lacking in another. For these reasons, little has been said of corticotrophin or thyrotrophin. All preparations of growth (diabetogenic) hormone tested depressed sensitivity to tuberculin and this is in keeping with our finding that diabetogenic agents tend to desensitize. But all these preparations, including those for which a high degree of purity was claimed, contained corticotrophin in appreciable amounts. However, desensitization produced by growth hormone differs from that produced by corticotrophin in being independent of ascorbic acid metabolism, unaffected by previous treatment with propylthiouracil and, in addition, by acting synergistically with cortisone (Cornforth and Long, 1953). There is, therefore, something other than corticotrophin in these comparatively crude preparations that depresses sensitivity to tuberculin. In general, diabetogenic agents depress sensitivity to tuberculin (Long, 1954b) so that it is likely that the desensitizing agent is growth (diabetogenic) hormone, but proof must await isolation of the substance. If then these observations are confirmed, the analogy between sensitivity to tuberculin and susceptibility to diabetes will be further strengthened.

SUMMARY (TABLE III)

Bacterial infection produces a short stage of invasion, toxæmia and destruction of tissue associated with adrenocortical hyperactivity and catabolism. With the development of immunity, a long stage of anabolism and repair is associated with a decrease in adrenocortical activity and increased insulin production.

TABLE III.

INFLUENCE OF HORMONES ON SENSITIVITY TO TUBERCULIN AND ANTITOXIC IMMUNITY IN GUINEA-PIGS.

Hormones	Sensitivity to tuberculin (bacterial allergy)	Synthesis of diphtheria antitoxin (antitoxic immunity)
Cortisone.....	↓ Reduced†	No effect
Corticotrophin.....	↓ Reduced†	? No effect?
Thyroxine.....	↑ Increased	↑ Increased
[Propylthiouracil.....	No effect*	↓ Decreased]
Insulin.....	↑ Increased†	? ↑ Increased
Growth hormone.....	↓ Reduced†	Uncertain

*Prevents desensitization by cortisone.
†Immediate effect.

There is a clear-cut species difference in response to "stress" or adrenocortical stimulation. Man, monkey and guinea-pig show greater endocrinological stability than the rat, mouse, rabbit or ferret. These species are also divided in their susceptibility to delayed bacterial allergy of the tuberculin type, in resistance to cortisone, in inability to synthesize ascorbic acid and in the non-protein-SH content of the carcass.

Thyroxine-treated guinea-pigs are more sensitive to intradermally injected tuberculin and produce more diphtheria antitoxin than control animals. Cortisone depresses sensitivity to tuberculin in both thyroxine-treated and control guinea-pigs, but is without significant effect on antitoxin synthesis. Insulin increases sensitivity to tuberculin, but, owing to the compensatory phenomena induced, a direct study of the effect of insulin on antitoxin production cannot easily be made. However, partial pancreatectomy abolishes both hypersensitivity and hyperimmunity resulting from treatment with thyroxine. The ratio of insulin to cortisone output profoundly influences the immune and allergic responses of guinea-pigs to bacterial infection.

It is unlikely that the influence of hormones upon sensitivity to bacterial allergens will indirectly affect the response of the guinea-pig to bacterial antigens.

The influence of hormones upon sensitivity to tuberculin is intimately concerned with ascorbic acid-sulphydryl metabolism.

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RÉSUMÉ

L'infection bactérienne produit une courte période d'invasion, de la toxémie et de la destruction des tissus reliées à l'hyperactivité du cortex surrénal et du catabolisme. Avec le développement de l'immunité, une longue période d'anabolisme et de récupération se manifeste en relation avec une diminution de l'activité du cortex surrénal et une augmentation de la production d'insuline.

Les diverses espèces montrent des différences bien marquées dans leur réaction à l'agression ou à la stimulation du cortex surrénal. L'homme, le singe et le cobaye présentent une plus grande stabilité endocrinienne que le rat, la souris, le lapin ou le furet. Ces espèces réagissent avec une même divergence dans leur sensibilité à l'allergie bactérienne retardée du type tuberculeux, dans leur résistance à la cortisone, dans leur impuissance à synthétiser l'acide ascorbique et dans le contenu sulphydrique non protéinique de leurs cadavres.

Les cobayes traités à la thyroxine sont plus sensibles à l'injection intradermale de tuberculine et produisent plus d'antitoxine diphthérique que les animaux témoins. La cortisone diminue la sensibilité à tuberculine chez les animaux de ces deux groupes, mais reste sans effet déterminé sur la synthèse de l'antitoxine. L'insuline augmente la sensibilité à la tuberculine, mais, à cause des phénomènes de compensation qui se produisent, il n'est pas facile d'étudier directement l'effet de l'insuline sur la production de l'antitoxine. Cependant, la pancreatectomie partielle supprime l'hypersensibilité et l'hyperimmunité résultant du traitement par la thyroxine. Le rapport quantitatif de l'insuline à la cortisone exerce une influence profonde sur les réactions allergiques et l'immunité des cobayes à l'infection bactérienne.

Il est peu probable que l'action des hormones sur la sensibilité aux allergènes bactériens puisse influencer indirectement la réaction du cobaye aux antigènes bactériens. L'influence des hormones sur la sensibilité à la tuberculine est étroitement liée au métabolisme de l'acide ascorbique et des groupes sulphydriques.

M.R.D.

FREQUENCY OF THE ASYMPTOMATIC
LOWER OESOPHAGEAL CONTRACTILE
RING

A ringlike narrowing or constriction in the terminal portion of the oesophagus has been reported by several observers as occurring in 1-2% of unselected gastrointestinal examinations. The nature of the ring is uncertain. Most of these patients are asymptomatic but some complain of dysphagia in varying degree.

In 100 unselected gastrointestinal examinations (unselected except that patients with dysphagia were excluded) P. Kramer (*New England J. Med.*, 254: 692, 1956) found one oesophageal ring in six. Finding such a ring in a patient with dysphagia is not enough to explain the swallowing difficulty, unless the examiner demonstrates that barium capsules or barium mixed with food are arrested at the ring with characteristic symptoms.

RADIOACTIVE GOLD IN MALIGNANT EFFUSIONS*

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J. C. F. MacDONALD, M.A., Ph.D.

THE INSERTION of radioactive colloidal gold, Au^{198} , into malignant pleural and peritoneal effusions is a method that has been in use now for several years. Dosage values have been described by Walton and Sinclair¹ and King *et al.*,² metabolism and distribution of Au^{198} by Andrews *et al.*,³ and cellular changes in effusions have been discussed by Stembridge *et al.*⁴ This communication does not purport to be a survey of the literature, but rather an account of the experience in the Department of Radiotherapy, Toronto General Hospital.

In April 1952, permission was obtained from the Isotopes Committee, University of Toronto, to undertake a study of the results of insertion of this material into malignant effusions. From that time to November 30, 1954, a total of 101 patients have been treated with Au^{198} .

The radioactive gold colloid used in this work has been obtained from two sources—Charles E. Frosst and Company of Montreal, and Abbott Laboratories, Chicago, U.S.A. Supplies from both firms have been uniformly satisfactory. The Canadian colloid, which we have used whenever available, is prepared from pure gold-197 foil or wire irradiated in the Chalk River NRX reactor, to produce an activity at shipping time of about 30 mc. per millilitre. It is prepared in a pyrogen-free 0.1% gelatin solution, using ascorbic acid as a reducing agent. Alkali sufficient to give a final pH of 8 is used. The solution is stable when diluted with water, saline and many other solutions. Natural colour is a deep cherry-red, indicating a particle size of about 0.003 microns. There has been no evidence of appreciable amounts of active material precipitating out during shipment and handling. Both firms charge for millicurie shipped, which means that the user bears the cost of any transportation delays. For this reason a Canadian supplier is to be preferred in our case, since shipment is overnight by rail. The adoption of

this technique as a routine procedure, with the patient bearing the cost where possible, has had its effect upon the administration method.

The cost per millicurie from supplier is on a sliding scale; the greater the number of millicuries per shipment, the lower the cost. Thus, in order to minimize the cost to the patient, it is desirable to administer gold colloid to a number of patients in a single day from a single shipment. In practice we have found that this number is limited to four with the facilities at our disposal.

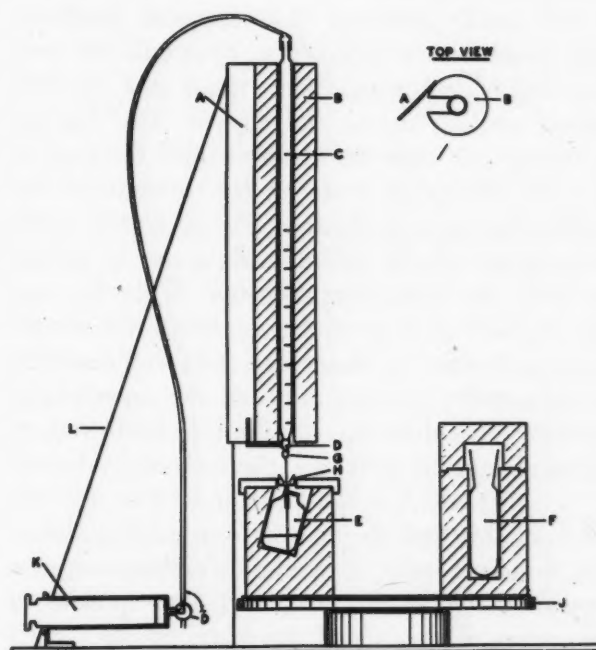


Fig. 1.—Dispensing apparatus. A—45° mirror; B—lead shield; C—25 ml. burette; D—metal valve; E—shipping bottle; F—administration bottle; G—fine needle; H—large bore needle; J—turntable; K—50 ml. syringe; L—support stand.

The shipment is received on the morning of the day of administration, and the total activity is roughly checked against the invoice by means of a large ionization chamber instrument. Use of this and of more accurate methods has given us a high degree of confidence in the figures of the supplier. The specific activity at the estimated time of administration is then calculated from the data available, and from this are obtained the volumes of colloidal fluid necessary for the various therapeutic doses.

The 50 c.c. sterile shipment bottle is then transferred to a special lead pot (Fig. 1), which is mounted on a rotatable table. At other points around the periphery of the table are four other lead pots of wall thickness 1 inch (2.5 cm.) designed to hold the 80 c.c. administration bottles.

*From the Department of Radiotherapy and Ontario Institute of Radiotherapy, Toronto General Hospital. An address given to the Section of Radiology, B.M.A., C.M.A., O.M.A. Joint Annual Meeting, Toronto, June 23, 1955. This project was supported by a grant from the Ontario Cancer Treatment and Research Foundation.

Supported over the table is a 1 inch thick lead sheath (B), surrounding an axial hole which can accept a 25 millilitre burette (C). The sheath is notched as shown in the section to allow the scale on the burette to be read by the 45° mirror (A) from the front. To the base of the burette a Luer lock is permanently affixed, which allows a valve (D) and a No. 20 needle to terminate the burette. The needle is long enough to reach to the bottom of the bottle, and the end is ground flat. A piece of plastic tubing leads from the top of the burette to a 50 c.c. syringe (K) through a two-way tap (D).

The sterile seal on the shipping bottle is punctured with a special No. 15 needle (H) and the bottle and surrounding lead pot is then swung around on to the sheath. The burette assembly can now be lowered until the end of the No. 20 needle rests on the bottom of the bottle. By opening the tap (D) and withdrawing the syringe (K) the colloidal fluid can be drawn up into the measuring burette. With the tap closed the burette assembly is raised, the administration bottles in their lead pots are revolved in turn under the burette, and the appropriate number of cubic cm. of fluid is delivered to them. The lead pots are then clearly labelled as to content. A small aliquot (a few mc.) is taken at this time for comparison purposes later. Six hundred mc. of gold-198 colloid can be broken down in this way with an exposure to the operator's hands of less than 10 mr.

The whole of the assembly is mounted on a stainless steel cart. When the above procedure is completed, all contaminated glassware, etc., is removed to a safe enclosure and the lead sheath and its support are removed from the cart. The turntable carrying the administration bottles and the syringe (H) and tap are used in the administration procedure.

INSERTION

The insertion procedure employed is extremely simple and involves a minimum of discomfort to the patient and of radiation exposure to the administering personnel. Radioactive contamination is negligible, except to the actual administration equipment.

The pleural or peritoneal cavity is tapped, using a standard thoracic aspiration tray and a No. 16 to No. 18 needle. Paracentesis needles are never used, because the large puncture has been found to permit leak-back of the gold col-

loid. If much fluid is present, either the patient is aspirated a day or two previously, or a longer time is allowed for removal through a No. 16 needle.

When aspiration is complete, the needle is left in place, and the equipment shown in Fig. 2 is connected to it by a convenient length of

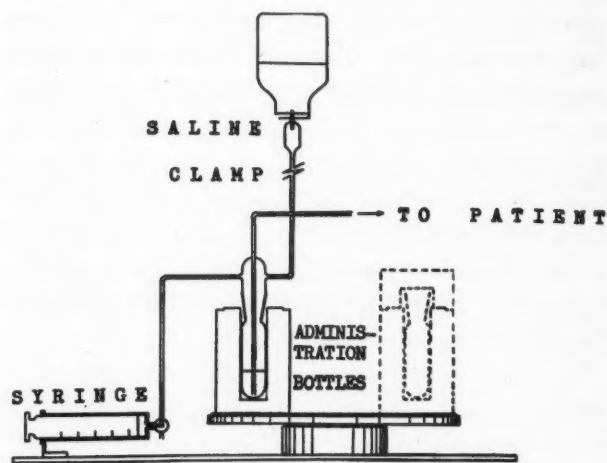


Fig. 2.—Insertion apparatus.

disposable tubing. With the saline connection clamped off, a slight withdrawal of the syringe brings fluid from the cavity into the transparent tubing if the needle is properly in place. Immediately after this precautionary check, the gold colloid is forced rapidly from the administration bottle into the patient by means of the syringe. This introduces into the cavity an amount of air equal to the volume of the vinyl tubing (approximately 1 to 2 c.c.). This is not considered to be undesirable, since the air fluid level created is an aid to even distribution during the subsequent motion of the patient. After the injection of the colloid, two washes of 50 c.c. of saline are forced through the system into the patient, thus reducing residual activity in the equipment and assisting in the production of an even distribution of colloidal particles within the cavity. The needle is then removed and the puncture sealed with a collodion dressing. All contaminated equipment and materials are removed to heavy paper bags and stored until decay permits re-use.

The patient is then required to change position every five minutes for the next hour, to allow gravity to assist in the dispersion of the radioactive material in the cavity. A rough scan of the patient with an ionization chamber instrument completes the procedure, and gives

a guide to radiation protection requirements in nursing the patient.

Dosage was begun at a rather low level, 35 mc. for chest, 75 mc. for abdomen. This has gradually been increased over the past three years, and now we use 100 mc. for chest and 200 mc. for the average abdominal case.

COMPLICATIONS

Several complications have ensued in the routine use of this rather simple procedure. It was found early in this series that the large puncture made necessary by the use of a paracentesis needle was difficult to seal after the needle was removed. A drawn stitch was necessary to stop leaking of the fluid, which still oozed during the first twelve hours. There was much radioactive contamination of dressings, bed and the floor of the room. Since that time only thoracentesis needles have been used, usually No. 16 or No. 18.

In one patient a pleural effusion was aspirated rather too completely before administration of radioactive gold colloid. On insertion she began to cough and spat up a few drops of red-stained sputum. This was tested with a Geiger counter and found to be highly radioactive. We concluded that the gold colloid had accidentally been injected into the alveoli. She was watched carefully, and coughed no more radioactive sputum in the following few days. Actually she had a surprisingly good result, the diagnosis being melanotic sarcoma with secondaries in the pleura. She had many thoracenteses before the administration of gold colloid, and none whatever after the insertion until death nine months later.

On one occasion the clamp on the tubing to the saline bottle was not firmly shut after the administration procedure was complete, and saline continued to drip unnoticed into the empty gold bottle. The bottle filled up and then overflowed the administration cart, scattering radioactive material widely over its surface. For this reason screw clamps are considered safer than the thin aluminum foil type that are supplied with standard intravenous sets.

All connections in the administration apparatus must be strong enough to resist the pressure used in transferring the colloid. On one occasion a joint became disconnected accidentally, and extensive contamination of equipment and hands resulted. Rubber gloves are now worn by all

administration personnel during these procedures.

Few patients have experienced more than temporary radiation upset, and those usually from abdominal insertion. One patient had a generalized dermatitis of moderate severity two weeks after insertion of 150 mc. into the abdomen. This was considered by the dermatological consultant to be a possible gold dermatitis. It yielded satisfactorily to conservative care.

Probably the worst complication, interstitial insertion, has not thus far been encountered. Before gold insertion we now draw back on the syringe a little to make sure the effusion fluid comes back into the tubing, thus indicating that the needle is in fact in the desired bodily space.

POST-INSERTION INVESTIGATIONS

Scanning

It is of interest to determine the distribution of radioactive material within the cavity, in order to ensure that the effect will be produced over the whole of the cavity and not in a single small volume of it. This determination should be done after the colloid has had sufficient time to become evenly distributed, and yet before the dose already delivered is so great as to render senseless its removal in the event of loculation.

While the scanning method used to date is in many ways unsatisfactory, it does give a clear indication of loculation. The method is essentially as described by Walton and Sinclair.⁵ One day after administration the patient, supine or prone on a stretcher, is bridged by a stand supporting a large lucite plate. An Anton Geiger-Mueller tube in a suitable directional shield can be moved in a known way over the surface of the plate, and the detected activity made to register on a scaler and count-rate meter. While this method is crude and is being improved, it is exact enough to give the information desired (Fig. 3).

In most hospitalized cases, aliquots of the first two or three 24-hour urine samples are counted in fixed geometry and an estimate of activity in the excreta is obtained. Similarly if tapping is necessary in the first two or three weeks after administration, the activity remaining in the fluid can be determined. If it is assumed that all the fluid present at the time of aspiration has been removed, the activity in the fluid can be expressed as a percentage of the total activity instilled, corrected for decay to the

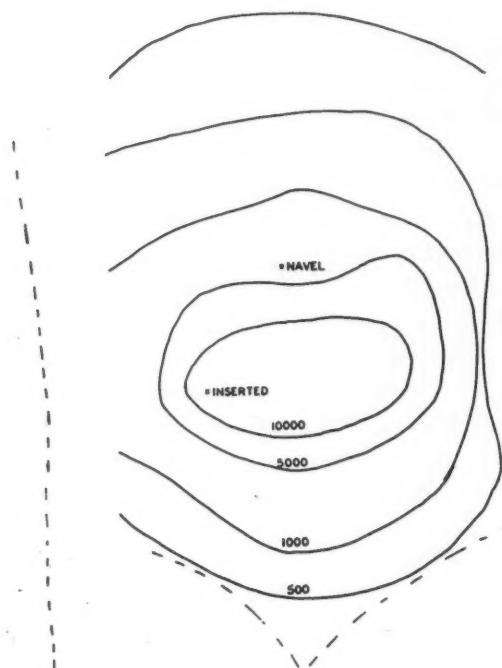


Fig. 3a.—Normal distribution.

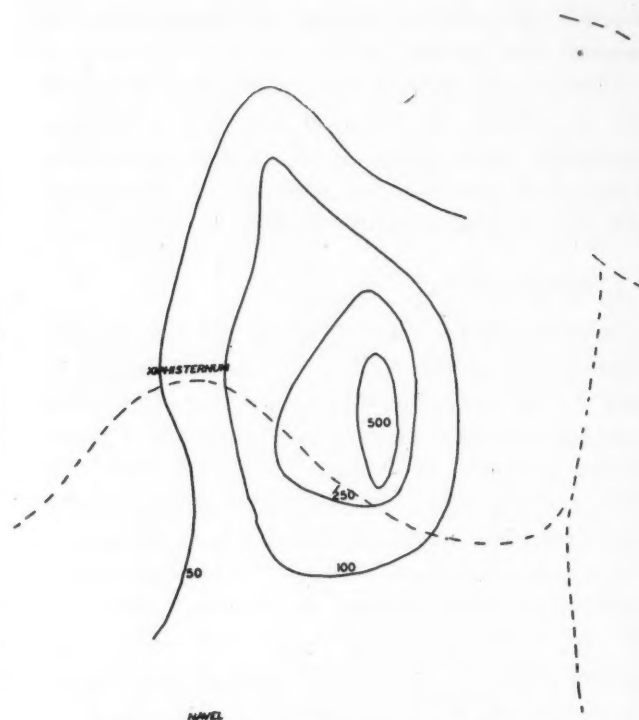


Fig. 3b.—Loculation (numbers are counts/min.).

time of removal. Table I shows the results obtained in this way for 11 patients.

Since urine and faeces samples collected and counted during the first few days after instillation have invariably shown extremely low activity (maximum $0.09 \mu\text{c}/\text{c.c.}$ for urine), and blood

TABLE I.

PERCENTAGE IN SAMPLE OF TOTAL ACTIVITY REMAINING
AT TIME OF REMOVAL

Fluid	MC. instilled	Interval in days	C.C. removed	Percent
Pleural	70	9	1,000	4%
"	100	8	1,000	3-6%
"	100	7	?	3%
"	100	6	750	2%
"	100	7	1,000	3%
"	100	7	1,000	3%
"	100	8	2,400	3.5%
"	80	7	150	negligible
"	100	8	400	2%
Peritoneal	180	10	8,600	10%
"	200	12	4,500	3.5%

samples of two representative patients have shown even lower activity, it is reasonable to assume that the majority of the active material is deposited either in the serous surfaces or in the liver, spleen and kidneys. Serial samples removed at intervals after instillation in two patients have roughly confirmed the above findings.

RESULTS

At the Dunlap Building, Toronto General Hospital, a total of 101 patients had gold insertions up to November 30, 1954. Patients who have had this treatment since then are not included in this report. A number of these patients had more than one gold insertion into chest or abdomen, or both, so that there was a total of 116 instillations of Au^{198} in this time into these 101 patients. Patients were considered improved by the Au^{198} insertion if either no further aspirations of fluid were needed or the frequency of aspirations was reduced drastically. All others, including those who died too soon for assessment, were considered failures.

The largest single group was of patients with carcinoma of breast. The results with these malignant effusions treated with Au^{198} are summarized in Table II.

TABLE II.

CARCINOMA OF BREAST			
	No. of instillations	Improved	% improved
Chest instillations . . .	44	22	50%
Abdominal instillations	6	0	0
Total instillations . . .	50	22	44%

There were 43 patients who had these 50 instillations. Three patients had two unsuccessful chest instillations; two patients had double chest instillations, the second many months after the first for a slow reaccumulation of fluid. Two patients had both abdomen and chest instillations for fluid formation. Slightly less than half were judged as improved.

Cases of carcinoma of the ovary with malignant effusions were the second largest group. The results are shown in Table III.

TABLE III.

CARCINOMA OF OVARY			
	No. of instillations	Improved	% improved
Chest instillations...	7	4	
Abdomen instillations.....	14	3	
Total instillations....	21	7	30%

These 21 instillations were in 18 patients, since one had bilateral chest fluid, one had two instillations into the chest without success, and one had abdomen and bilateral chest instillations, all unimproved. Results here were somewhat disappointing, especially in the group with ascites. Only 3 out of 14 instillations were judged as improving the condition, the over-all picture being 30% improved compared with 44% for breast.

Somewhat surprisingly good results were obtained in the group with secondary carcinoma of pleura or peritoneum, primary unknown. The 20 insertions of gold are summarized in Table IV. Half were judged as improving the condition.

TABLE IV.

SECONDARY CARCINOMA: PRIMARY UNKNOWN			
	No.	Improved	% improved
Chest instillations.....	9	4	
Abdomen instillations.....	11	6	
Total instillations.....	20	10	50%

These 20 instillations were into 16 patients, 4 having double instillations. Miscellaneous diagnoses are tabulated in Table V.

It may be noted that three instillations were undertaken in two patients with pleural effusion, not proven as associated with cancer. The patients were not helped in the least; the final

TABLE V.

MISCELLANEOUS DIAGNOSES			
Instillations			
Bronchogenic carcinoma	7	(1 into abdomen)	only 2 improved
Lymphoma	7	all chest	only 1 improved
Fibrosarcoma	1	chest	improved
Melanotic sarcoma	1	chest	improved
Carcinoma cervix	3	all abdomen	none improved
Carcinoma bladder	1	chest	unimproved
Carcinoma uterine body	1	abdomen	improved
Non-malignant	3	chest	all unimproved (possibly cardiac)

diagnosis was of probable cardiac failure, and the cases are not included in the total of 99 patients with malignant effusion.

Results in lymphoma were quite disappointing, in view of the usual response to radiation. In four of this group, however, death ensued so quickly that the gold may not have had time to be effective.

The last table, Table VI, summarizes the total results of instillation and the number of patients improved. The two figures are virtually the same, i.e. 40%.

TABLE VI.

TOTAL INSERTIONS IN MALIGNANT EFFUSIONS			
	No.	Improved	% improved
Chest instillations.....	80	35	44%
Abdomen instillations.....	36	10	27%
Total instillations.....	116	45	39%
Total patients.....	99	40	40%

One factor which has not been discussed had a bearing on these results, namely, death ensuing before the gold had time to act. When this work was begun, all patients were accepted for this type of treatment, since it was not felt that we had reliable criteria of rejection. However, no less than 21 patients of the 99 were judged as having died too soon for the gold to act, usually within the month. It is now clear that this procedure should never be used on cachectic or very ill patients, as it does take some time to give results. The patient is being put to needless expense and trauma unless he has a reasonable chance of surviving at least several months. In no case has the instillation clearly prolonged life, the use being only to re-

lieve the symptoms of rapidly reaccumulating fluid.

It has thus far been found difficult if not impossible to predict which patients will be helped by the treatment. From the various tables, it can be seen that good results are sometimes obtained in unexpected cases. As mentioned before, results in metastatic ovarian carcinoma have been disappointing. One patient not included in this survey, since she was treated within the last six months, had a rather good regression after insertion of 100 mc. directly into a malignant ovarian cyst.

In patients with abdominal masses plus fluid, the masses have shown no change as the result of the insertion of Au¹⁹⁸, and we feel that these patients are better treated by external radiation.

In four patients who had suppression of fluid after the first instillation of gold, with slow reaccumulation many months later, some success was attained with a second instillation of gold. Two of the effusions were pleural, two peritoneal. However, in eight cases where the first instillation of gold failed to control the reaccumulation of fluid, a second dose of radiation delivered by Au¹⁹⁸ failed again. In four patients who had insertions into both chest and

abdomen, no pattern of failure or success could be shown.

CONCLUSIONS

As in all new treatments for cancer, initial hope has given way to more modest expectations. Some conclusions have been arrived at after the observation of these 101 patients:

1. To obtain any results, the patient must be in reasonable health, not cachectic.
2. The method should be used only when withdrawal of fluid results in prompt reaccumulation on several occasions.
3. Second insertion of Au¹⁹⁸ should not be contemplated unless the first insertion has clearly suppressed fluid formation for many months.
4. The method holds reasonable (40%) chance of relief of the distressing symptom of persistent fluid reaccumulation in malignant disease. The most favourable responses have been in cases of cancer of breast with persistent pleural effusion.

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MITRAL VALVULOTOMY— RESULTS OF A PRELIMINARY SURVEY IN 104 CONSECUTIVE CASES*

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WITHIN THE LAST FEW YEARS the surgical management of selected cases of rheumatic mitral disease has achieved a more firm footing. From the earnest prophecy of Lauder Brunton¹ at the turn of the century, the experimental and clinical endeavours of Tuffier,² Cutler and Levine,³ Cutler and Beck,⁴ Smithy,⁵ Souttar,⁶ Harken,⁷

Bailey⁸ and many others, there has arisen an operative procedure which in less than a decade has gained universal acceptance. This acceptance has cast a further responsibility on the cardiologist in the selection of those patients who will benefit by surgical treatment.

PHYSIOLOGICAL CONSIDERATIONS

Although rheumatic heart disease is pathologically speaking a pancarditis, once beyond the acute stage, valvular involvement is the most common basis for clinical manifestations. Advances in our knowledge of the disturbed physiology in patients with mitral stenosis have been furthered by the more general application of cardiac catheterization both clinically and in the laboratory.

Normally the mitral valve orifice exhibits a cross-sectional area of 4 to 6 square centimetres, and offers little or no measurable resistance to

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flow of blood from left atrium to left ventricle. Furthermore, the entire pulmonary circuit is a low-pressure system with a gradient of only 5 to 10 mm. Hg between the pulmonary artery and left atrium. This relatively small resistance of the pulmonary bed reflects itself in the tremendous increases in flow which may normally occur without significant increases in pulmonary artery pressure. Cournand⁹ has demonstrated that little or no alteration of pulmonary artery pressure may occur until the flow exceeds two and one-half times normal.

Gorlin's¹⁰ correlation of theoretically constructed pressure flow curves with mitral valve area has indicated that in patients with mitral stenosis in whom the mitral area is 2.5 sq. cm. or greater, symptoms of pulmonary congestion are absent. In these patients, over a twofold increase in cardiac output can be tolerated without symptoms, and in them pulmonary venous pressures are almost invariably less than 35 mm. Hg. Furthermore, Dexter¹¹ had shown that a pulmonary wedge pressure of 35 mm. Hg is the critical level at which clinical pulmonary oedema appears. In those patients whose mitral areas were between 1.5 and 2.5 sq. cm., only mild symptoms were present, while areas less than 1.0 sq. cm. were invariably associated with crippling limitations. Complicating factors such as pulmonary vascular disease and heart failure may significantly modify these relationships. Gorlin¹⁰ has suggested that a 2.5 sq. cm. mitral orifice valve area should be the objective goal in patients undergoing surgery for mitral stenosis. It may be conclusively stated that the disability of patients with mitral stenosis arises primarily from the engorgement of the pulmonary circulation which in turn reflects itself in the classical symptoms of the disease, i.e. dyspnoea, cough, orthopnoea, haemoptysis and pulmonary oedema. It is this mechanical barrier to the flow of blood through the stenosed mitral orifice that present-day surgical measures are designed to correct. The most widely accepted procedure is that of mitral commissurotomy, which was developed in the hands of Bailey⁸ and co-workers.

CLINICAL DATA

As in all fields of clinical endeavour, the efficacy of any treatment rests in the consistent benefit obtained in a significant series of patients. The literature has borne witness to in-

creased numbers of reported series¹²⁻¹⁸ of patients who have undergone mitral surgery. The following is a report, albeit a relatively short-term one, of the first 104 consecutive patients who underwent mitral surgery at the University of Minnesota Hospitals between December 1950 and January 1954. The operative procedures were carried out by twelve members of the teaching and resident staff. The majority of these patients have been followed up by return visits to the cardiac clinics; a few were contacted by questionnaire and letters from their referring physicians. The longest period of follow-up was just over three years; the shortest, four months. There have been no deaths in the above-mentioned follow-up period; however, there has been one late death in a patient operated on 22 months ago. Approximately one-third of the group have been investigated by cardiac catheterization both before and after operation for the objective assessment of such features as cardiac output, pulmonary artery and wedge pressures, and blood volume. These findings¹⁹ have already been reported in part. A survey of the more general features of this group of patients shows that the majority were between the ages of 30 and 50 (Table I). The youngest was 10 years of age, the oldest 62 years, with a mean of about 40. Although advancing years in themselves do

TABLE I.

AGE DISTRIBUTION						
0-10	11-20	21-30	31-40	41-50	51-60	61-70
1	5	15	28	40	12	3
Youngest—10 Oldest—62 Average age—39 - 40.						

not constitute a barrier, it is more generally agreed that, as a group, patients aged 45 and under will obtain the greatest benefit with less surgical risk. The sex distribution of this group is in keeping with that of other reported series. There were 30 males and 74 females, a ratio of 2.5:1.

In attempting to obtain some uniformity in classifying these patients before and after operation, we have chosen to follow the criteria set up by the American Heart Association.²⁰ The functional capacity nomenclature refers primarily to the assessment of cardiac disability in terms of the patient's symptoms and signs. The therapeutic assessment, on the other hand, inter-

TABLE II.*

FUNCTIONAL CAPACITY	THERAPEUTIC CLASSIFICATION
<i>Class I.</i> Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain.	<i>Class A.</i> Patients with cardiac disease whose ordinary physical activity need not be restricted.
<i>Class II.</i> Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.	<i>Class B.</i> Patients with cardiac disease whose ordinary physical activity need not be restricted but who should be advised against severe or competitive physical efforts.
<i>Class III.</i> Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnoea or anginal pain.	<i>Class C.</i> Patients with cardiac disease whose ordinary physical activity should be moderately restricted, and whose more strenuous efforts should be discontinued.
<i>Class IV.</i> Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome are present even at rest. If any physical activity is undertaken discomfort is increased.	<i>Class D.</i> Patients with cardiac disease whose ordinary physical activity should be markedly restricted.
	<i>Class E.</i> Patients with cardiac disease who should be at complete rest, confined to bed or chair.

*Nomenclature and Criteria for the Diagnosis of Diseases of the Heart and Blood Vessels. 5th ed. N.Y. Heart Assoc. Distributed by the Am. Heart Assoc., 1775 Broadway, New York 19, N.Y.

prets the functional capacity in terms of each individual's everyday living and his ability to carry on therein. For clarity these two methods of assessment are reproduced here (Table II).

Reference to Table III indicates the results of surgery as interpreted in terms of the patient's functional capacity. As shown, almost one-third of the group were Class IV patients before surgery.

TABLE III.

RESULTS—FUNCTIONAL CAPACITY CLASSIFICATION						
Preop. classn.	No.	Postop. classn.				Operative deaths*
		IV	III	II	I	
IV.	31	4	5	14	1	7
III.	54	—	6	24	22	2
II.	16	—	—	4	12	—
I.	3	—	—	—	3	—

*Death from the time of induction of anaesthesia to discharge from hospital.

This figure is seemingly high, but it encompasses a fair number of desperately ill patients who were submitted to operation at this institution with little alternative early in the surgical history of mitral stenosis. The mortality rate of 22% is in part a reflection of the advanced disability of this group. One patient died during induction of anaesthesia, three died during operation and the remaining three in the postoperative period. Despite this seemingly heavy cost, at least one-half of this group obtained significant improvement. Those patients who were in Class III preoperatively obtained the most significant improvement; some 40% of them (postoperative Class I) obtained excellent results, which rendered them almost symptom-free. An additional 45% (Class II) were also benefited to the extent of having only minimal cardiac limitation. The number of patients in Classes I and II is small, about one-half being operated on primarily for recurrent embolization. In all, 28 of 104 patients had one or more major peripheral or pulmonary emboli before operation. None of these patients had any clinical episodes to suggest embolization during the period of postoperative follow-up. Examining the whole group one finds that 75% obtained benefit as a result of the surgical intervention in the course of their disease. The mortality for the group was 8.7%, a figure which compares favourably with other reported series.²¹ The surgical morbidity comprised one case of permanent grossly incapacitating cerebral infarction, several cases of postoperative pleural effusions which responded readily to aspiration, and one case of lung hernia.

TABLE IV.

RESULTS—THERAPEUTIC CLASSIFICATION							
Preop. classn.	No.	E	Postop. classn.			A	Operative deaths*
			D	C	B		
E	27	4	3	6	7	—	7
D	37	—	5	8	16	8	—
C	34	—	—	2	21	9	2
B	4	—	—	—	1	3	—
A	2	—	—	—	—	2	—

*Death from time of induction of anaesthesia to discharge from hospital.

As shown in the therapeutic classification of assessment (Table IV), an even greater number of patients were rehabilitated to the point where they could manage their daily tasks. The un-

satisfactory results, in the 12 patients in Classes D and E, correspond roughly to those in Classes III and IV of the functional capacity assessment. On the whole, the therapeutic classification is a more subjective one and therefore tends to yield a higher percentage of satisfactory results. As indicated earlier, this method is based on the patient in his environment, and his ability to carry on in it within the limits of his cardiac reserve.

SURGICAL TECHNIQUE

There was nothing unusual in the technical aspects of the operative procedures carried out in this series of cases. The thoracotomies are performed with the patient in the lateral decubitus position, through a 4th or 5th transcostal incision. The pericardium is opened along the line of the phrenic nerve and marsupialized by a series of traction sutures. The base of the left atrial appendage is then secured with a heavy silk purse string and, after application of a non-crushing auricle clamp, the auricle is opened and generously flushed out in an attempt to minimize embolization. The commissures are palpated and forcibly separated. In about 20% of cases in this series it was necessary to introduce a commissurotomy knife in order to overcome extensive fibrosis or calcification at these sites. Bilateral external carotid pressure is applied during the valvular manipulations but we have no evidence to suggest that this manoeuvre will prevent or minimize the danger of cerebral embolization. The commissures are opened with the intent of providing an orifice at least 2.5 sq. cm. in area. Finally the auricular appendage is tailored and oversewn with silk mattress sutures, its remainder being excluded from the auricular chamber by tying the previously placed silk purse string at its base. All cases are drained by catheter-suction for a period of 36-72 hours postoperatively.

Postoperative care entails the routine use of antibiotics, and careful attention to fluids, which are given by mouth if at all possible; otherwise a limit of 1,500 c.c. by vein is imposed as a working rule. Coughing is insisted upon and encouraged by naso-laryngeal catheter suction. Digitalization and low sodium diet are maintained in those instances where they have been instituted in the preoperative care of the patient.

DISCUSSION

Through the years much has been written regarding the pathogenesis, diagnosis and management of mitral disease. However, it is only more recently, through such careful studies as that of Wilson and Greenwood,²² that we have obtained more factual data on the natural history of mitral stenosis. Their findings indicate quite clearly that the degree of valve deformity correlates well with the disability present. Following the onset of severe pulmonary congestion or auricular fibrillation, 50% of these patients were dead within five years, and 80-90% had succumbed within 15 years. The appearance of right heart failure exacted a 50% attrition within three years of its onset. Studies such as this should serve to revise some of the older thinking on the course of mitral valve disease which all too often represented the experience of one physician whose clinical acumen was not supplemented by detailed long-term follow-up. On the other hand, many of the observations^{23, 24} documented by cardiologists earlier in this century have been confirmed by the findings of more recent surveys; namely, that heart size and functional capacity are better indications in prognosis than the character and loudness of the murmur. The advent of left heart catheterization has also demonstrated that the murmurs may give very little reliable information about the degree of stenosis or regurgitation.

The selection of these patients for mitral valvulotomy had as its basis those individuals having relatively "pure" mitral stenosis with significant disability and pulmonary hypertension. These findings could be arrived at through the correlation of the clinical, radiographic and electrocardiographic findings, combined in some cases with cardiac catheterization studies. The presence of aortic valvular disease need not in itself constitute a contraindication unless a degree of regurgitation is present with more than minimal haemodynamic effects. As indicated earlier, the presence of embolic phenomena was a clear indication for surgical management even in the absence of incapacitating clinical symptoms.

The results of this follow-up indicate that somewhere between 75 and 80% of patients who are carefully selected for mitral valve surgery can expect improvement. This improvement is subjective (dyspnoea, exercise tolerance) and is usually correlated with a

diminished pulmonary hypertension and disappearance of hæmoptysis or frequent episodes of sudden pulmonary oedema. Many will tolerate complete relaxation of dietary salt restriction and/or limitation of physical activity. It has been repeatedly pointed out that immediate clinical improvement is often out of proportion to the benefit which could possibly be derived from the degree of stenosis which was found and relieved at operation. This was undoubtedly true in a minority of these patients and serves to emphasize the necessity of prolonged follow-up in order to minimize the physiological influences which surgery can evoke. However, even if these factors could be wilfully eliminated, there will remain a small residue of individuals manifesting prolonged and unquestionable benefit despite the fact that at operation only a minor degree of stenosis was encountered. What subtle role the pulmonary circulation may play in this group is but a mere speculation. Notwithstanding, it would appear that the best results may consistently be expected in those individuals with disabling symptoms associated with significant pulmonary hypertension. These patients, when combined with those who are suffering repeated embolism, constitute that group of mitral stenosis patients in whom the indications for surgery are most clear-cut.

A second reassessment of this group of patients is now contemplated and should serve to define some of these factors further.

SUMMARY AND CONCLUSIONS

1. The preoperative and postoperative assessment of a group of 104 patients subjected to mitral valvulotomy has been presented.

2. A few of the basic concepts of the disturbed physiology of patients with mitral stenosis are mentioned.

3. In terms of functional capacity and therapeutic classification, between 75 and 80% of the entire group manifested improvement. In addition, between 35 and 40% of patients had excellent results, being restored to unlimited activity without clinical symptoms.

4. The over-all mortality was 8.7%. Aside from one instance of severe morbidity due to massive cerebral embolization, the other postoperative complications were of a comparatively minor nature in keeping with those of thoracotomy for non-cardiac procedures.

5. The selection of patients with mitral stenosis for valvulotomy is an individual problem based on an over-all assessment of symptomatology, physical signs, radiography and electrocardiographic studies; in some instances, cardiac catheterization may be necessary. The presence of disabling symptoms with significant pulmonary hypertension, and a history of repeated embolism, are two of the major indications for surgery.

6. The importance of successive prolonged follow-up in assessment of cases is emphasized.

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RÉSUMÉ

L'auteur présente l'évaluation préopératoire et postopératoire d'un groupe de 104 malades ayant subi une valvulotomie mitrale. Quelques principes fondamentaux portant sur les troubles physiologiques des mitraux sont évoqués. En terme de capacité fonctionnelle et de classement thérapeutique, 75 à 80% du groupe montrèrent de l'amélioration. De plus, 35 à 40% des malades obtinrent d'excellents résultats, reprenant une activité normale sans manifester de symptômes cliniques. L'intervention comporte une mortalité de 8.7%. Si l'on fait exception d'un cas d'embolie cérébrale massive, le degré de morbidité causé par les autres complications post-opératoires est assez bas et de l'ordre de celle que l'on rencontre dans les thoracotomies chez les non-cardiaques. Le choix des malades atteints de sténose mitrale comme candidats à la valvulotomie est basé sur une évaluation totale de la symptomatologie, des signes physiques, des études radiologiques et électrocardiographiques; dans certains cas, le cathétérisme du cœur peut être nécessaire. La présence d'hypertension pulmonaire ainsi que celle d'embolies multiples sont des symptômes dont la gravité constitue une indication pour l'opération. L'auteur insiste sur l'importance de l'observation prolongée des malades dans leur évaluation.

M.R.D.

A NEW DRUG FOR ALCOHOLISM TREATMENT

I. A NEW DRUG FOR THE TREATMENT OF ALCOHOLISM

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FOR THE LAST EIGHT YEARS disulfiram (Antabuse) has been used widely as an adjunct in the treatment of alcoholism.¹ Opinions vary as to its importance in the management of alcoholic patients but in many clinics it has a valued status in spite of certain unpleasant characteristics.^{2, 3} In 1953 an investigation was begun with support from the Alcoholism Research Foundation of Ontario to find a drug which, like disulfiram, would render the effect of alcohol unpleasant to the drinker but might be free from some of the disagreeable features of disulfiram which now discourage some patients from continuing with its use.

Most of the substances known to alter the effects of ethyl alcohol contain sulfur.⁴ None of these were investigated since it seemed likely that all such substances would impart an unpleasant odour to the breath or perspiration or cause an unpleasant taste in the mouth, all of which have been grounds for complaint against disulfiram. One compound known to have the desired action but unlikely to decompose into malodorous substances was carbimide (cyanamide). Carbimide possessed another advantage. Its compounds have been used industrially for many decades with remarkably few toxic effects apart from their well-known effect of inducing a disagreeable reaction to alcoholic beverages. The syndrome caused by alcohol after carbimide has been called "mal rouge". It is characterized by intense flushing of the face and neck and often of the whole body, accompanied by a rapid pulse, a pounding heart and panting respiration. At this stage acetaldehyde can be tasted or smelt by the subject on his own breath. Nausea and vomiting sometimes follow and in more severe reactions a precipitous fall in blood pressure may occur, particularly if the patient attempts to sit up or stand up. The severity of the reaction depends on the amount of carbimide in the system and the amount of

alcohol taken. A severe reaction is a terrifying experience, but the more dramatic symptoms usually subside in a few hours and the patient is usually none the worse after 24 hours.

Carbimide itself is not suitable for use as a drug because it is too hard to obtain in quantity in a pure state, and because it is too unstable. For this reason a number of compounds of carbimide of greater stability were investigated.*

METHODS

Tests for activity were mostly done on animals, but from time to time these were confirmed by tests on human volunteers. The criteria for activity in animals were: (1) measurement of acetaldehyde in the blood of rabbits, rats and mice by the method of Burbridge, Hine and Schick;⁵ (2) measurement of "bleeding weight" in rats and mice. To do this the abdomen was opened under anaesthesia and wiped dry. The aorta and vena cava were cut. The blood was absorbed in a dental sponge which was previously weighed when dry and was weighed again immediately after the blood had stopped flowing.^{6, 7} Bleeding weights were expressed as a percent of body weight. In normal rats and mice the bleeding weight (B.W.) is 4.0-4.5%. If the chest is squeezed gently towards the end of the bleeding, somewhat higher figures are obtained, e.g. up to 5%. After disulfiram or carbimide followed at a suitable interval by ethanol (1 c.c. of a 10% solution by volume per 100 g. of body weight) the B.W. fell often to levels of 3.0-3.3%.^{8, 9} This reaction proved a more reliable indicator of a typical action on humans than did the elevation of blood acetaldehyde alone.

For the tests on humans it was important to keep the dose of ethanol small, so that the reaction would be definite but not so severe that the subject would be discouraged from trying it again. Fifteen c.c. of ethanol diluted with water and taken on an empty stomach is a good test dose. The onset of the reaction is fairly rapid, i.e. in about 10 minutes, and over in 30-45 minutes. After a meal, the reaction to the same dose of alcohol is delayed. There is a temptation then to take another drink or two. When the reaction finally develops, it may be unpleasantly severe and prolonged.

OBSERVATIONS

The derivatives of carbimide which were tested most thoroughly included dicyandiamide, chloroformamidine, monosodium carbimide and calcium carbimide. The first two were not sufficiently active to be useful. The monosodium salt was too alkaline to be taken in a capsule or as a tablet. Calcium carbimide was tolerated if taken in acidified solution but gave rise to vaguely unpleasant sensations which passed off in about one hour. These sensations were attributed to effects of carbimide on the central nervous system when the drug was absorbed too rapidly. They were reduced or eliminated when the drug was administered in a tablet specially designed to release the drug slowly.

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*Kindly supplied by the American Cyanamid Co., Stamford, Conn.

A dose of 50 mg. of calcium carbimide, followed in three to 15 hours by a test dose of alcohol, was found by the writer to give rise to sharp reactions on several occasions. When ethanol in doses up to 50 c.c. was taken 24 hours after the carbimide, the reaction was very mild. When the dose of calcium carbimide was increased to 100 mg., two subjects experienced definite reactions to test doses of alcohol 30 and 36 hours after taking the carbimide.

In small animals (rats and mice) the elimination of the carbimide seemed to be rather more rapid. No definite effects were observed when the test doses of ethanol were given 24 hours after the carbimide.

In rats and mice doses of 10 to 20 mg. of carbimide result in large rises of blood acetaldehyde after test doses of alcohol. Larger doses, viz. 75-100 mg. per kg., are required to lower the B.W. after alcohol.⁸ The LD50 of carbimide given orally as acidified calcium carbimide but expressed as mg. of carbimide per kg. of body weight was found to be 320 for rats and 510 for mice.⁸

MODE OF ACTION OF DISULFIRAM OR CARBIMIDE

The oxidation of ethanol in the body proceeds by steps. One of these is oxidation to acetaldehyde. The amount of acetaldehyde in normal human blood is scarcely detectable, i.e. less than 0.05 mg. per 100 c.c. After ingestion of an alcoholic beverage the blood acetaldehyde increases to figures of 0.2-0.4 mg. per 100 c.c. or even higher. If disulfiram or carbimide is given in suitable doses before the alcoholic beverage, the blood acetaldehyde rises to much higher levels.^{10, 11} Disulfiram and carbimide inhibit one or more enzymes which are required to oxidize acetaldehyde.^{12, 13} Asmussen, Hald and Larsen¹⁴ concluded that the typical effects of disulfiram followed by alcohol, viz. vasodilatation, tachycardia and hyperpnoea, were due simply to the increased concentration of acetaldehyde. It now seems that this is not the whole story.^{9, 11} The sensitizing drugs not only cause an accumulation of acetaldehyde after alcohol ingestion but may also alter the vascular reaction to acetaldehyde.

An experiment to illustrate such an effect can be done very simply on the skin of the forearm. Exposure of the skin to a high concentration of acetaldehyde vapour causes only a slight local reaction. If, however, a small area of skin is previously treated with carbimide or disulfiram, exposure to acetaldehyde vapour causes an intense flushing localized to that area.

It has been pointed out already that the action of carbimide persists for only one day, or at the

most two days, in humans. The effects of disulfiram are known to last for a week or longer. There is also a difference between these drugs in the speed of onset of their sensitizing action. So far with carbimide, all subjects have been sensitized by a single dose of 50 or 100 mg. of calcium carbimide. With disulfiram a single dose may or may not be effective. Some patients have been known to take 0.5 g. of disulfiram daily for one week or even two weeks without being sensitized to alcohol. If such a patient drinks at this time and experiences only a mild reaction, he is likely to conclude that he must be immune to the drug. He may try drinking more freely at a later date, with dire consequences.

It is hard to say why there is such an irregular period of latency with disulfiram. The experiments of Divatia, Hine and Burbridge¹⁵ indicate that the drug is absorbed fairly rapidly from the alimentary tract. It is, however, much more soluble in fat than in aqueous solutions. Perhaps the fat depots take up most of the drug for some period before sufficient amounts can accumulate in the circulation to produce the characteristic effect.

CITRATED CALCIUM CARBIMIDE,*

A PREPARATION OF CARBIMIDE

Calcium carbimide dissolves only slowly in water and with decomposition to form ammonia. The formation of ammonia can be prevented by dissolving the calcium carbimide in an acid solution. For use as a drug, it is necessary to present the calcium carbimide with sufficient acid to neutralize the calcium and provide additional acid to keep the pH of the medium below 4 or 5. Citric acid in two parts by weight to one part of calcium carbimide was found to be suitable. At this point a warning must be given against the use for medicinal purposes of technical grades of calcium carbimide (calcium cyanamide). The technical grades have been found to contain many dangerous impurities including cyanides. Highly purified calcium carbimide was kindly prepared for us by North American Cyanamid Ltd., Niagara Falls, Ont. It contained 96-98% of calcium carbimide, the residue being mainly calcium carbonate.

It was mentioned earlier that rapid absorption of carbimide from the alimentary tract may pro-

*To be marketed under the registered name Temposil, by Lederle Laboratories Inc.

duce unpleasant sensations not easily described. To avoid these it was necessary to incorporate the calcium carbimide and citric acid in a slow-release tablet. A suitable tablet was developed by Lederle Laboratories Inc., Pearl River, N.Y. It is important to distinguish between a slow-release tablet and a slowly disintegrating tablet. In the earlier stages of the development, a tablet was produced which disintegrated very slowly but which allowed, much more rapidly, the leaching out of the carbimide. With this tablet the sensations characteristic of rapid absorption of carbimide were all too evident. The non-proprietary name recommended is "tablets of citrated calcium carbimide" for this preparation of purified calcium carbimide with citric acid in a slow-release tablet, each containing 50 mg. of calcium carbimide.

CLINICAL TRIALS

Clinical trials of citrated calcium carbimide are in progress in the Bell Clinic, Willowdale, Ont., and the Brookside Clinic, Toronto. Preliminary reports of these trials appear on pages 795 and 797 of this issue; experience to date has been sufficiently encouraging to warrant this preliminary description of the new preparation and its properties.

Subjects who have experienced the effects of disulfiram and alcohol and of carbimide and alcohol could not see any difference between them. For this reason the same warnings which apply to the use of disulfiram should apply to citrated calcium carbimide. Frivolous or unsupervised use of either drug must not be tolerated. On the other hand, it is expected that the new drug, used under medical supervision, will be safe and free from many troublesome side-effects of disulfiram.

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II. A NEW PROTECTIVE DRUG IN THE TREATMENT OF ALCOHOLISM (PRELIMINARY CLINICAL TRIAL OF CITRATED CALCIUM CARBIMIDE*)

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THIS IS A BRIEF REPORT on initial experience at Brookside Clinic with a new drug in the treatment of alcoholism. Citrated calcium carbimide (CCC) has been developed¹ in an attempt to find a drug which has all the beneficial attributes of disulfiram (tetraethylthiuram disulfide), commonly known as Antabuse, with elimination of its drawbacks, which are, essentially: (a) an inconsistency of the unpleasant reaction experienced when alcohol is taken by a person using the drug, and (b) a number of unpleasant side-effects apart from the reaction with alcohol. This initial report is concerned solely with comparing the side-effects of CCC with those of disulfiram. Later studies will be concerned with the nature and reliability of the reaction when alcohol is taken.

During the period of trial, 19 patients were started on CCC (Table I). Ten of the 19 patients were on CCC 21 days or longer, two of the patients being on the drug for a period of approximately four months. Thirteen patients were given a dose of 50 mg. daily. Six received doses of 100 mg. daily for periods of from six to 25 days. Fifty mg. is considered to be the daily dose for the average patient.

Seven of the patients had been previously on disulfiram and had a variety of complaints with that drug—drowsiness, nausea, impotence, and unpleasant taste. None of the patients who had complained of drowsiness on disulfiram had unpleasant symptoms on CCC. In fact, one patient indicated a feeling of comfort better than in previous periods of sobriety when taking no

*It is understood that CCC will be available under the registered name Temposil.

†Brookside Clinic, Alcoholism Research Foundation (Toronto).

TABLE I.

	CCC	Disulfiram
Total patients	19	33
Patients reporting back for study	19	17
Percentage	100	51
Patients reporting after three weeks	10	5
Percentage of group followed up	53	29
Patients reporting for four months	2	1
Percentage of group followed up	10.5	6
Patients on recommended protective dose	12	6
Percentage of group studied	63	35
Patients on $\frac{1}{2}$ or less of recommended protective dose		11
Percentage of group studied		65
Patients on <i>double</i> recommended dose	6	0
Percentage of group studied	32	0
Patients reporting <i>new</i> side-effects:		
drowsiness alone	1	1
nausea and drowsiness	0	2
Patients reporting relief of symptoms on CCC:		
impotence disappeared	1	
drowsiness disappeared	4	
taste disappeared	1	
Patients reporting continuing symptoms:		
impotence*	2	

*Not considered due to CCC (see text).

drug. Another complained of nightmares and fitful sleeping on 100 mg. daily which disappeared when the dose was reduced to 50 mg. daily. One patient who had complained of both drowsiness and impotence on disulfiram, suggested that he felt more than ordinarily stimulated sexually after starting on CCC. Two other patients who had complained of impotence noted no difference; one of these continued to be impotent when his drug was later switched to an inert placebo. The other patient who continued to be impotent was found to have a suppression of his spermatogenic activity, which presumably had taken place while he was on disulfiram, or possibly even before he started the drug. The one patient who complained of unpleasant taste while on disulfiram had no such symptom on CCC. He did report after approximately 10 weeks that he had drunk rum while on CCC, with no effect. Unfortunately, we have not seen him since that time and have been unable to carry out a reliable trial of this reported reaction. One patient who complained of feeling drowsy refused to take disulfiram, stating that he could carry on without assistance.

For comparison we can consider 33 patients started on disulfiram during the same period. More patients were given disulfiram, since in the initial phase of the study CCC was offered only to those who had previously been on disulfiram and had discontinued it by reason of some unpleasant effect. The dose given was 500 mg. daily, reduced to 250 mg. if symptoms of drowsiness appeared.

Of the 33, only 17 returned for follow-up evaluation beyond a few days' initial observation in hospital. Two of these reported feeling drowsy and nauseated to such an extent that the dose of drug was reduced to 125 mg. daily. A third also complained of drowsiness but carried on. Other complaints were not encountered in this small series. An additional eight patients had their dose of disulfiram reduced to 250 mg. daily because of slight feelings of drowsiness.

DISCUSSION

From this brief study, one gains the impression that CCC is at least a useful substitute for disulfiram with some patients who have had unpleasant side-effects on that drug, in that these effects were not experienced with the second drug. One gets the general impression, also, that there is an over-all reduction in the frequency of side-effects with this drug. It is difficult, of course, to rely on these observations when one considers the relatively high degree of follow-up so far with the CCC group and the marked failure of patients in the comparison group on disulfiram to return for continued observation. Maybe a high incidence of side-effects caused patients to turn against the drug and fail to return to the clinic. On the other hand, it is very likely that there is a considerable element of suggestion associated with introducing CCC, and that the fact of being on a new and interesting drug may have induced the CCC group to return for follow-up. Motivation, or its absence, is a problem to be considered in any group of alcoholic patients.

This would point up the need for a very carefully controlled long-term study of CCC, with disulfiram and a placebo for comparison, in a blind study, in order to analyze more carefully the nature and incidence of the side-effects produced. There has often been reason to suspect that many of the side-effects reported by patients were the result of suggestion, even though there

is probably a true incidence of the particular side-effect in a lesser number of patients.

CONCLUSION

This study suggests that citrated calcium carbimide is useful as one of the group of protective drugs in the treatment of alcoholism. Even if there were no reduction in the frequency of side-effects, CCC appears to have value as a substitute for disulfiram in patients reporting unpleasant side-effects with the older drug. However, it would also appear that there are fewer side-effects with CCC and that it may be the drug of choice.

In the present study no attempt has been made to determine the nature of the reaction when alcohol is taken by a patient using the drug CCC, although other evidence¹ suggests that CCC fulfils the criteria which make disulfiram a useful drug.

The results to date are sufficiently encouraging to warrant continued investigation.

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III. CLINICAL TRIAL OF CITRATED CALCIUM CARBIMIDE

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IN NOVEMBER 1955, Antabuse (disulfiram) was discontinued at our clinic in order to institute a clinical trial with citrated calcium carbimide. As of today (March 12, 1956) 64 patients have been given the new preparation in a dosage of 1 tablet (50 mg.) daily; 51 of these patients were men, and 13 women.

Twenty-six patients had formerly been treated with Antabuse; 23 of them claimed that they had experienced undesirable side-effects while taking the drug, such as drowsiness, weakness, unpleasant taste, unpleasant breath, body odour, or impotence. The side-effects from the new preparation appear to be practically nil.

At the beginning of the experiment a few patients complained of stomach distress shortly after taking the tablet. This appeared to be overcome effectively by administering the tablet

after a meal. Two patients complained of rheumatoid pain, but in one this cleared up without discontinuing the medication. The other patient discontinued the drug and, to date, we have not had an opportunity to test her reaction to the drug more thoroughly. One patient claimed that his eyes were sore while taking the drug, cleared up when he stopped, became sore again when he started the medication and cleared up permanently when he discontinued the medication altogether. This is an out-of-town patient and I have had no opportunity to observe this reaction at first hand. None of the 64 patients complained of drowsiness, headache, bad breath, body odour, unpleasant taste in the mouth, or impotence. To the best of my knowledge, only the two patients mentioned have discontinued using citrated calcium carbimide because of symptoms they attributed to the drug.

Several years ago we discontinued giving a test with alcohol after Antabuse had been administered for a few days. This policy was continued with the new preparation. However, two patients attempted to drink 24 to 36 hours after their last dose of the new preparation. Both described very unpleasant effects, similar to what would have occurred had they tried to drink following Antabuse medication. One patient thought that we were exaggerating the undesirable effect of alcohol after administration of citrated calcium carbimide, and deliberately drank a double martini within a few hours of taking a tablet. He was more than impressed with the result and described symptoms of flushed face, rapid heart, and shortness of breath, followed by nausea and general malaise.

DISCUSSION

The first two years of abstinence are considered to be the period of greatest unpredictability. We believe that it is a period in which, with proper medical supervision, frequent feedings, and dietary supplements of protein and the water-soluble vitamins, a new state of metabolic stability can be attained. We believe that in the interval many patients will experience unpredictable states of extreme tension or depression which cannot be wholly explained by their psychological problems. These episodes are often referred to by the patients themselves as "dry drunks". The states of restlessness and discomfort experienced by patients at such times frequently play an important role in relapses.

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We believe it important for patients to be able to take a preparation which will make their reaction to alcohol undesirable until this period of re-stabilization is passed. I am convinced that patients can undo, by a few days' drinking, the "state of repair" that may have taken several months to achieve. Accordingly, we like our patients to acquire a sufficient understanding of the hazards in the first two-year period of abstinence to welcome the added protection of a disulfiram-like substance. It is pointed out to all patients that the taking of such a drug does not in any way replace the need for active participation in other aspects of a rehabilitation program, including association with Alcoholics Anonymous or other phases of the follow-up program at the clinic itself. It had been suggested to all patients that they should take disulfiram for from 18 to 24 months. Very few would continue taking it for that length of time. Accordingly, we were very much pleased to participate in the clinical trial with the new preparation.

Our experience after four months' continuous use of citrated calcium carbimide leads us to the following interim conclusions.

1. Citrated calcium carbimide is less toxic than tetraethylthiuram disulfide (Antabuse) and is much better tolerated by patients as a result. Accordingly, there is real hope that more patients will continue using the drug for the

length of time considered important in launching a rehabilitation program.

2. As reported elsewhere in this paper, the protection afforded the patient by citrated calcium carbimide is almost instantaneous. If alcohol were taken, it is likely that there would be fewer delayed and possibly dangerous reactions with this drug than with disulfiram.

3. Since the new preparation is more rapidly eliminated from the body, it does not provide the carryover of protection for three or four days which frequently occurred when disulfiram was discontinued. However, in my opinion, this carryover of protection is of no great significance because patients who discontinue disulfiram in order to drink, do not change their minds after two to three days without the drug.

SUMMARY

Sixty-four patients were given citrated calcium carbimide (CCC) in doses of 50 mg. daily by mouth, as a substitute for disulfiram; 26 had previously had disulfiram and 23 of them had had unpleasant side-effects. None of the 64 patients had these effects with CCC, though two discontinued the drug for other reasons. Results of a test dose of alcohol were similar to disulfiram reactions. Protection with CCC is instantaneous but there is no carryover on stopping the drug.

ADVANCED BREAST CANCER

A SMALL SERIES TREATED BY HYPOPHYSECTOMY*

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THE TREATMENT OF advanced mammary cancer involves a bewildering complexity of difficulties. Many of these patients are in constant pain, their general condition is poor, and their mental

outlook on life is depressed. These difficult patients will come to any general surgeon in the hope that help can be given them.

The majority of treatments at present (with the exception of local x-radiation) are on an endocrine basis, involving particularly the secretions of the ovaries and adrenals.⁹ Recently, investigation has begun on the role of the pituitary gland in cancer, especially in cancer of the breast.^{3, 11}

The rationale of hypophysectomy for advanced cancer rests on a combination of theory and empirically proven fact. In so far as theory is concerned, we must first consider the concept of "hormone-dependent tumours". This concept implies that tissues, such as breast, that are normally dependent on hormones for growth

*This paper is a result of the collaboration between the Departments of Neurosurgery, Metabolism and Biochemistry and the Breast Section of the Nova Scotia Tumour Clinic at the Victoria General Hospital. Before hypophysectomy is offered, the patient is seen in consultation by individual members of the departments concerned and then is discussed in a group meeting when a decision is made. We feel that this collaboration is essential since each department is vitally concerned in totally different aspects of a difficult problem.

and function, can give rise to tumours that are similarly dependent.⁸ Consequently, withdrawal of the specific hormones involved would cause regression of such a tumour. The supportive hormone in question here appears to be oestrogen, which may be produced by the ovaries or adrenals, and it has been shown in a number of series that removal of these glands has a beneficial effect in a fair proportion of cases.⁹

A considerable amount is known concerning the reciprocal relationship of the pituitary and its so-called "target-glands"—the thyroid, ovaries, and adrenals. Diagrammatically, this is shown in Fig. 1. Here the solid lines denote the stimulating trophic hormones of the pituitary, and the broken lines represent the hormones of the individual target glands, which have a controlling or depressing action on the pituitary.

It follows then that removal of the pituitary with its trophic hormones can be expected to depress markedly the function of the target glands. Provided that breast cancers are dependent on the hormones of these glands, such a procedure should be of benefit.

Segaloff and his co-workers, after much investigation on endocrine treatment of breast cancer, have stated that only those hormonal agents, such as methyltestosterone or oestrogen, that are capable of lowering the gonadotropin production of the pituitary⁶ have given significantly good results.

However, the oestrogen level is not the complete answer to breast cancer. Experiments on hypophysectomized animals have shown that this procedure decreases the incidence of spontaneous² and induced tumours,⁴ and lessens the incidence of "take" of transplanted tumours.⁶ The tumour-restraining influence, however, is not totally due to depression of function of the "target glands", since this restraining effect can be *only partially* nullified by replacement therapy with various pituitary hormones,² cortisone, etc.

So it is a possibility that some as yet unknown pituitary factor has a supportive effect on cancer,⁵ or that this effect may be related to interaction of the hormones with which we are familiar, particularly growth hormone, ACTH, and possibly thyroid hormone.¹

Hypophysectomy then may have beneficial results, since the activity of all the target glands will be lessened and any other hypothetical factors of the pituitary will be removed.

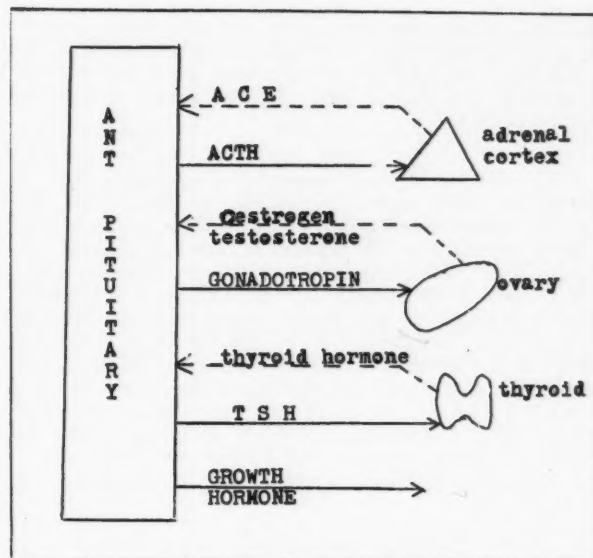


Fig. 1.

PRESENT SERIES

The cases reported here were all far advanced when first seen at our Breast Clinic, directed by Dr. N. H. Gosse, and could be considered only for palliative treatment. The hypophysectomies were done by Dr. Stevenson of Halifax. The most important preoperative and postoperative metabolic care, which we consider to have been a very important factor in the smooth course of these patients, was carried out by Dr. Tanning of Halifax. Every case had an uneventful postoperative course, with no complications of any importance. Maintenance therapy consists only of $\frac{1}{4}$ - $\frac{1}{2}$ grain of thyroid and 12.5-25 mg. of cortisone daily.

CASE 1.—The first case was in a woman of 41, admitted in March 1954. On admission she complained of a lump in the left breast which had been present for a year, and back pain present for 2-3 months. This pain was so severe that she had been bedridden for the preceding month.

Examination showed a large ulcerating mass involving most of the left breast and extending into the axilla. The axillary and supraclavicular nodes were grossly involved, and there were several subcutaneous nodules palpable in the skin of the abdomen. Radiography showed involvement of the ribs, pelvis, and lower thoracic and upper lumbar spine. The pertinent laboratory findings were: alkaline phosphatase level up to 44 units per 100 ml., and 17-ketosteroid excretion of 8.9 mg. a day. Biopsy showed undifferentiated cancer. On April 1, 1954, a hypophysectomy was done. As an interesting finding, histological examination of the removed gland showed the presence of secondary carcinoma. Within three weeks of operation, she was free of pain, and the axillary and supraclavicular lymph nodes had almost disappeared. Three months later, she had no complaints of any sort, was doing her full housework, and the primary lesion was much smaller. X-rays now showed marked regeneration in the metastatic deposits. This good result has continued, and when last seen 19 months postoperatively, she stated that

she felt better than ever. The primary lesion has disappeared completely, and regional lymph nodes are not palpable. The alkaline phosphatase level has returned to normal and the 17-ketosteroid excretion is less than 1 mg. a day.

CASE 2.—Our second case was considerably less encouraging. This patient, admitted in June 1954, had had a radical mastectomy followed by x-ray therapy a year previously. On admission she complained of a lump in the remaining breast and severe low back pain which had been present for several weeks. Examination showed that the lump complained of probably was a local recurrence. X-ray survey showed involvement of the lungs only. The laboratory findings indicated only some rise in alkaline phosphatase level. A hypophysectomy was done on June 22, 1954. Postoperatively her pain was considerably relieved. She was discharged home to return for further metabolic studies, but died two months postoperatively of carcinomatosis.

CASE 3.—The third patient had had a radical mastectomy and postoperative x-radiation in 1950. She had no further complaints until four years later, when she developed back pain. X-rays showed metastatic deposits in the spine. She was then treated with testosterone and local x-radiation with some minor relief. She was admitted in September 1954 with a pathological fracture of the right femur and severe recurrent back pain.

X-rays now showed increasing collapse of the involved lumbar vertebrae and an extensive deposit at the site of the fracture of the femur. Laboratory tests showed only a little rise in alkaline phosphatase level.

She had a hypophysectomy on October 11, 1954. Her progress to date has been fair, but not as good as we had hoped. Now 13 months postoperatively, she continues to be free of pain, but the bone lesions are not filling in. However, the lesions appear to be partially checked, she is comfortable, and we hope for some further progress.

CASE 4.—The next patient was a 54-year-old nurse admitted in October 1954 complaining of severe back pain. She had had a right radical mastectomy in February 1952, and two years later a left radical mastectomy for what probably was a secondary deposit. X-rays on admission showed involvement of the lumbar spine, pelvis and ribs. Hypophysectomy was done on November 25, 1954. Her postoperative course was uneventful. She was shortly transferred to another hospital, where she died five months later. Unfortunately, the record of this period is not very complete, but apparently she received little benefit from the procedure. She still complained of pain, and required fairly large amounts of sedatives until her death in May 1955.

CASE 5.—In this case the result so far appears to be good. This patient had had a radical mastectomy early in 1950. She had no further trouble until the summer of 1954, when she began to have back pain. X-rays at this time showed involvement of D 7 and 8, and L 5. In September 1954, a bilateral oophorectomy was done, and she was put on testosterone. This did nothing to relieve her pain and she was forced to keep to her bed because of it. Hypophysectomy on December 6, 1954, was followed almost immediately by relief of pain. She was allowed out of bed in six weeks, and thereafter her range of activities was rapidly extended. She was seen a week ago, 11 months postoperatively. She felt quite well and was engaged in her usual activities. However, although this patient feels well, has no pain, and has regained her initial weight loss of 45 lb., x-rays show that there is no great regeneration in the involved areas of the spine. Her alkaline phosphatase level has not changed remarkably.

CASE 6.—The history of this next case is essentially similar to the others. She had a radical mastectomy in 1952, and was well for two years. She then began to have severe back pain, and had been in bed for two months before she was admitted in December 1954. X-rays showed involvement of the spine, ribs and femur. Hypophysectomy was done in January 1955. Postoperatively, she was relieved of her pain but her general condition was only fair. Repeated radiographs showed extension of the lesions, especially in the femur. This patient died two weeks ago, about seven months postoperatively.

Six other operations have been done, but too recently for any evaluation. However, the result in one will be interesting, since the first evidence of cancer was a deposit found in the omentum during a routine Cæsarean section. Even with repeated careful examinations, the breast lump was not found until about two months thereafter.

So, in these cases, we have two excellent results, one fair and three poor. There appear to be no correlating factors that could be used preoperatively in estimating the chances of a good result.

In Table I are grouped the good, fair and poor results for comparison of some of the findings. The first two results are good, the next is fair, and the last three are poor. The histological examination of all cases showed undifferentiated carcinoma.

It is apparent that the result is not affected by the age of the patients, the duration and type of the primary lesion, the type of treatment (if any) preceding hypophysectomy, and the interval between the treatment of the primary and the appearance of the secondary lesions.

For example, one of our patients with a good result had no other treatment of any sort; the other had had a radical mastectomy followed by radiotherapy and later by an oophorectomy and testosterone administration. In one case with a good result, the apparent interval between the appearance of the primary and secondary lesions was nine months. In the other, the interval was about 48 months. In the poor results, the intervals were ten, three, and 22 months.

The one suggestive factor we have noted is that those patients in whom the distant spread is exclusively to bony tissue appear to have a better result. In the two good and one fair results, the distant spread was to bone only. Of the poor results, in one case there was spread to the other breast and lungs, and in one to the other breast.

TABLE I.

Case	Age	Duration of primary	Treatment preceding hypophysectomy	Secondary (site)	Interval between treatment of primary and appearance of secondary
1	41	12 months	nil	Spine Pelvis Ribs Lymph nodes	9 months
5	47	3 months	1. Radical mastectomy and x-ray ('50) 2. Oophorectomy and testosterone ('54)	Spine	48 months
3	42	2 months	1. Radical mastectomy and x-ray ('50) 2. Testosterone and x-ray ('54)	Spine Femur	48 months
2	44	1 month	Radical mastectomy and x-ray ('53)	Lungs Other breast	10 months
4	54	1 month	1. Rt. radical mastectomy and x-ray ('52) 2. Lt. radical and x-ray ('54)	Other breast Spine Pelvis Ribs	3 months or 24 months?
6	52	2 months	Radical mastectomy and x-ray ('52)	Spine Ribs	22 months

Consideration of the preoperative laboratory findings gives no real help in prognosis. In Table II it is seen that the alkaline phosphatase level is somewhat higher in the cases with good results, but we do not consider this to be particularly significant. The postoperative level has no relationship to the result. Study of steroid excretion before and after operation gave some surprising results. These results are so contrary to what we expected that if they are confirmed in future cases, we may have to revise some of our ideas. For instance, in one of our two good results the ketosteroid excretion level dropped to zero. In the other it rose from 0.4 to almost 8 mg. Of the three poor results, two patients showed a marked decrease and one showed an increase in ketosteroid excretion.

Even more surprising are the results of oestrogen determination. The first two patients, with a clinically excellent result, show oestrogen excretion within normal limits and, even more perplexing, the one with the higher excretion had had an oophorectomy done. Conversely, the third patient who is classed as having only a fair result has an oestrogen excretion well below normal.

The level of excretion of follicle-stimulating-hormone (FSH) is greatly below normal in all cases, as we had expected. This result probably indicates complete removal of the pituitary.¹¹ Again there is lack of correlation with the clinical result. Two of these patients are very good, and the third is only fair, but the FSH excretion is decreased equally in all.

TABLE II.

Case	Alk. phosphatase before after (units per 100 ml.)		17-ketosteroids before after (mg. per day)		Cholesterol before after (mg. per 100 ml.)		FSH excretion after (mouse units)	Oestrogen excretion after (micrograms a day)
1	44.0	3.8	8.9	nil	160	302	less than 6.6 m.u.	97
5	13.6	9.4	0.44	7.8		336	less than 6.6 m.u.	141
3	5.8	10.4	5.3	0.5	200	310	less than 6.6 m.u.	40
2	7.8	3.1	4.5	1.2	226	310		
4	8.0	22.0	1.3	4.3	280			
6	8.9	24.0	4.6	2.4				

As yet we can draw no conclusions, but we think this procedure has something to offer in the far-advanced cases where other, less radical, procedures have proven useless. Of the six cases reported, in two the disease appears to be arrested, and the patients are apparently healthy and happy, living a normal life with their families. A third patient, in whom the result has not been so successful, has been free of pain for a year now, and has a more hopeful outlook. Of the three who have died, two were relieved of their pain.

SUMMARY

Six cases of advanced breast cancer were treated by hypophysectomy. There were no

postoperative complications. Of the six results, two are considered excellent and one fair; three patients died, two, five and seven months post-operatively. Six other cases are too recent for evaluation.

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ANSOLYSEN* IN THE TREATMENT OF ARTERIAL HYPERTENSION†

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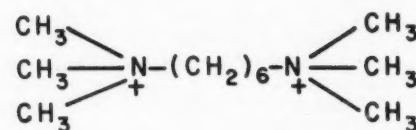
THE DISCOVERY in 1948 of hexamethonium and its hypotensive properties by Paton and Zaimis,¹ as well as the numerous clinical studies that followed, instigated a searching pharmacological study of the organic derivatives of quaternary ammonium compounds. In 1952, Libman, Pain and Slack² in the laboratories of May & Baker, London, synthesized several of these derivatives, nine of which were studied for their effects on man by Maxwell and Campbell.³ The most active was shown to be pentamethylene:1:5-bis-(1-methylpyrrolidinium), which is presented in the form of the bitartrate, Ansolsen.*

Ansolsen resembles hexamethonium chemically and pharmacologically (Fig. 1). They are both salts of bisquaternary ammonium compounds. The two nitrogen atoms are separated

in one case by five methylene (CH₂) groups and in the other case by six. Their mode of action is identical. They both act by blocking the transmission of nerve impulses at the level of the autonomic ganglia, competing with acetylcholine.⁴ Ansolsen and hexamethonium have, in addition to their hypotensive action, the same secondary effects which are often disagreeable to the patient; some of these effects are paralysis of accommodation, constipation which may become obstinate, dryness of mouth, impotence and orthostatic hypotension.

The ganglioplegic activity of Ansolsen, studied on the superior cervical ganglion of the cat, appears to be five times greater than that of hexamethonium, and its duration of action about 1½ times longer.⁵

ION HEXAMETHONIUM



ION ANSOLYSEN

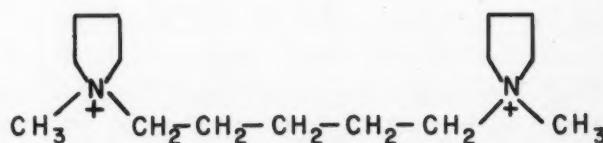


Fig. 1

*Generously supplied by Mr. Charles Desjardins, Poulenc Limited, Montreal.

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TABLE I.

SUMMARY OF RESULTS OBTAINED WITH ANSOLYSEN ADMINISTERED ALONE OR IN COMBINATION
STABLE ESSENTIAL HYPERTENSION

Patient	Age	Control	Ansolsen			+ Reserpine			+ Apresoline			+ Apres.		+ Reserp.	
			Time*	Upright	Horiz.	Time*	Upright	Horiz.	Time*	Upright	Horiz.	Time*	Upright	Horiz.	Time*
P.P.	44	207/113							17	192/89	194/87				
A.S.	40	181/139										10	156/115	164/104	
A.A.	70	201/108							13	164/93	209/95				
A.L.	50	252/127				17	199/105	208/114							
N.G.	48	239/110	7	221/115	222/115				8	191/91	202/92				
J.F.	50	248/131										14	203/101	221/102	
C.N.	60	242/129	16	162/100	170/97										
R.G.	55	201/108	26	169/94	197/108				20	171/93	198/104				
E.B.	55	200/120	11	205/114	207/107	28	167/100	190/103							
L.R.	49	238/129	6	196/105	219/130	17	191/106	207/117							
A.B.O.	50	209/118				11	234/124	232/120							
S.B.	40	221/133				6	142/93	180/104							
R.L.	39	212/140							16	227/126	233/138				
H.C.	46	212/135				56	197/106	222/105							
P.B.	39	189/121							24	154/106	161/102				
J.P.	63	247/136				13	152/94	188/102							
A.M.	37	192/124							56	154/101	171/105				
E.L.	43	248/120	6	187/110	209/115	48	165/98	176/98				9	178/96	181/106	
E.L.	55	227/111	17	204/87	231/90	9	158/68	183/66							
B.R.	30	226/130							25	171/112	196/118				
A.B.	55	191/108				6	166/95	189/92							
L.B.	45	250/117							13	222/120	198/109				

*Weeks.

The first clinical trials on hypertensive patients were made by Smirk^{6,7} and these were soon followed by others.⁸⁻¹¹ Here, we wish to report observations we have made on a group of hypertensives treated with Ansolsen alone, or Ansolsen associated with older hypotensive agents.

METHODS

Thirty patients, 22 of whom had essential stable arterial hypertension and 8 malignant hypertension, were submitted to treatment during periods ranging from 4 to 56 weeks. The treatment was generally preceded by a period of controlled observation of at least four to five weeks.

In the rare cases where this was not possible owing to the serious condition of the patient, the mean reading of the arterial pressure taken hourly during the first two days of hospitalization was used as control.

After their hospitalization, the patients were followed up each week at the hypertension clinic of the Hôtel-Dieu Hospital. The arterial pressure was taken at each visit, three times with the patient in the standing position, and three times in the horizontal position, by a specialized nurse, in accordance with the criteria of the American Heart Association. The arterial pressure of patients in hospital was taken hourly from 7 a.m. to 9 p.m. during their stay in hospital.

We administered Ansolsen either alone or with Apresoline and/or rauwolfia.

RESULTS

1. Effect on Blood Pressure

The effects of treatment on the arterial pressure of 30 patients are given in detail in Tables I and II. These tables show clearly that a lowering of arterial pressure, often spectacular, was observed in each case. This lowering is still more

TABLE II.

SUMMARY OF RESULTS OBTAINED WITH ANSOLYSEN ADMINISTERED ALONE OR IN COMBINATION
MALIGNANT HYPERTENSION

Patient	Age	Control	Ansolsen			+ Reserpine			+ Apresoline			+ Apres.		+ Reserp.	
			Time*	Upright	Horiz.	Time*	Upright	Horiz.	Time*	Upright	Horiz.	Time*	Upright	Horiz.	Time*
A.R.	23	217/125	10		168/102				3		185/108				
H.B.	51	228/127	21	118/72	209/112							9	137/75	219/104	
L.L.	3	236/136	5	138/94	220/126	9	122/90	246/140				8	192/106	210/108	
G.M.	46	213/132				21	133/97	200/108							
A.L.	29	216/142	4		158/116										
R.P.	46	233/146	6		230/129				15	191/127	215/126	37	176/105	204/113	
M.J.	28	210/132							6		174/107	15	157/100	187/113	
G.L.	21	212/156	18		184/127										

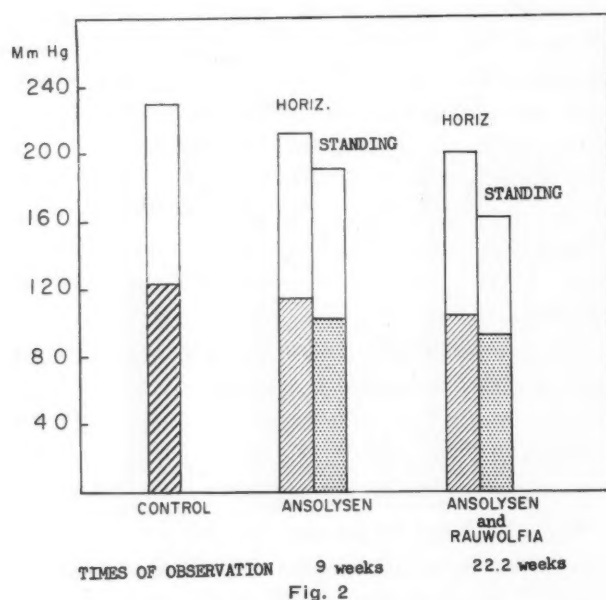
*Weeks.

TABLE III.

AVERAGE ARTERIAL PRESSURES					
Drug	No. of patients	Duration (weeks)	Control arterial pressure	Arterial pressure	
				Standing	Lying down
Ansolsen	12	11.9	227/128	178/99	205/114
Ansolsen + Rauwolfia	12	20.0	224/125	169/98	202/106
Ansolsen + Apresoline	11	19.3	215/123	185/106	195/107
Ansolsen + Rauwolfia + Apresoline	7	14.5	224/134	171/100	198/107

evident if it is compared with the average arterial pressures during periods of control and of treatment (Table III).

In five cases, we were able to compare the effect of Ansolsen alone with that of a combination of Ansolsen and rauwolfia (Fig. 2). The fall in pressure was more marked when Ansolsen was used in combination, the differential pressure being smaller, however. Figs. 3 and 4 show the action of Ansolsen, alone or



used in combination, during a period of several months, in one case of malignant hypertension and in one case of severe essential hypertension.

2. Modification of Ocular Lesions

Some authors^{14, 15} had previously reported that ocular lesions of severe essential hypertension and malignant hypertension had regressed with hypotensive therapy. The hæmorrhages, exudates and papilloedema disappear, which seems to indicate a reversal or at least a slowing down of vascular hypertensive processes.

Five cases of severe essential hypertension with a reduction of vision and hæmorrhagic

lesions and retinal exudate, have had regular ophthalmic examinations. In all these, we observed: (a) Complete and rapid (2 weeks on average) disappearance of hæmorrhages, this disappearance being final except in one case where there was a relapse. (b) Regression followed by complete absorption of exudate within 8-13 months.

In seven patients suffering from malignant hypertension with papilloedema, hæmorrhages and retinal exudate the lesions regressed rapidly and vision improved. In four cases the amelioration was maintained and the patients are still alive after 12, 13, 16 and 25 months of observation.* In three patients, there was a relapse of lesions, and these died in uræmia within a few months, without, however, any hypertensive encephalopathy or cerebrovascular accident.

3. Modification of Cardiac Volume

In seven cases of essential hypertension with left ventricular hypertrophy, the transverse diameter of the heart, measured before and after treatment, did not show any significant change except in one case (E.B.) where it had increased by 2.25 cm.

DISCUSSION

(a) Measure of Arterial Pressure

We wish to emphasize the importance of "nervous tension" when the patient visits the doctor's office or hospital. The arterial pressure of certain patients is at this time so much influenced by the anxiety of visiting the physician that we have been obliged in some cases to space out visits to the clinic as much as possible.

The case of Mrs. R.D. may be cited here.

At the beginning, she showed only slight response to hypotensive medication, her arterial pressure always being elevated during visits to the clinic. She informed us, however, of attacks of repeated weakness and dizzi-

*These patients have received other hypotensive drugs on occasion.

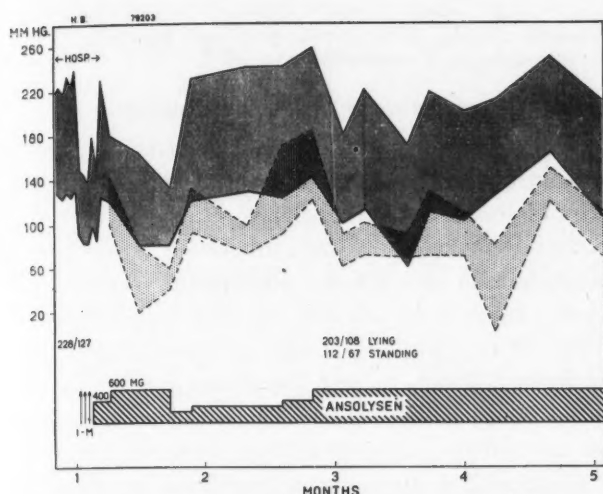


Fig. 3.—Mrs. H.B., aged 51, was referred in July 1954, complaining principally of frequent fronto-occipital headaches, dyspnoea upon moderate effort, decreased vision and frequent sensations of thoracic retrosternal constriction. Arterial pressure averaged 228/127; there was marked renal and cardiac dysfunction, bilateral papilloedema, some retinal haemorrhages and exudates. Ansolsen was first given parenterally with remarkable results, as can be seen from the graph. The patient was then given it orally for several months, with equal success. After some weeks, the retinal lesions and clinical condition improved considerably and the patient is still alive at the present time. Note the great difference between the arterial pressure taken in a standing position and in the horizontal position.

ness at home, bringing to mind an orthostatic hypotension. She finally confessed that coming to the clinic made her nervous and uneasy and caused her to have sensations of constriction difficult to describe. We then decreased her visits to the hospital, and had her pressure taken at home by her daughter, who was a nurse. We noticed, as in other cases, a marked difference between the higher readings taken at the clinic and the lower readings taken at her house. Without wishing to go so far as to show patients how to take their own blood pressure and to follow its course, we do believe that the nervous or anxious subject benefits from less frequent visits to the clinic and from surveillance at home by a member of the family or an outside person when possible.

As stated above, arterial pressure was taken with the patient standing and in a horizontal position. It is easy to observe the hypotensive action of the drug, especially on postural change. This activity moreover may vary appreciably from one subject to another (Figs. 3 and 4). One may therefore presume that the effect of hypotensive medication is practically of no significance when the patient is horizontal. Fortunately, in 296 patients at present attending and who have been visiting our clinic for a period of nearly two years, and of whom also more than one-third are receiving ganglion-blocking agents, we have not seen any hypertensive accidents while the patient was asleep or in a horizontal position. We have discarded as impractical the method proposed by Smirk⁶ which aims at making the patient sleep in an inclined position of 45°.

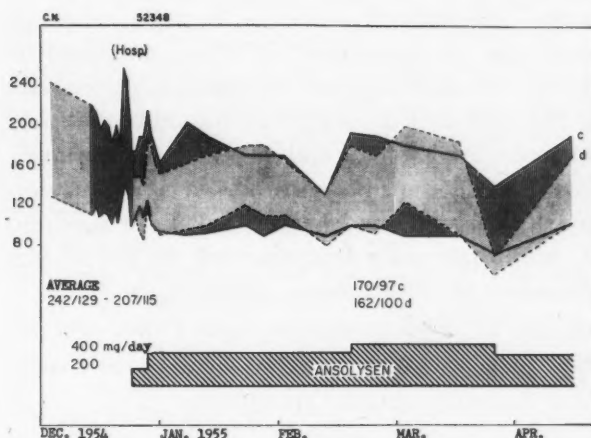


Fig. 4.—Mrs. C.N., aged 60, came to hospital in December 1954, complaining of headaches, of precordial pain, dyspnoea upon moderate effort, and insomnia, all progressively developing during a period of five years. She had good renal function, left ventricular hypertrophy, and fundus lesions of vascular sclerosis with tortuous vessels of irregular calibre. The average arterial pressure decreased from 242/129 mm. Hg (controlled before admission) to 207/115 during her hospitalization. The patient was given Ansolsen alone for over five months, and average arterial pressure fell to 162/100 mm. Hg (standing position). It is interesting to note, in contrast to Fig. 3, the small difference between arterial pressures taken in the standing and reclining positions.

(b) Dosage and Administration of Ansolsen

Ansolsen, being an exceedingly powerful hypertensive agent, must be used with caution. The initial dose is from 20-40 mg., taken 15 to 20 minutes before each meal and at bedtime, to ensure an even digestive absorption. Each dose is increased by 20-40 mg. four times a day at intervals of five to seven days until the desired hypotensive effect is obtained.

The maintenance dose varies generally between 160 and 800 mg. a day. Tolerance to Ansolsen seems to us to be less marked than in the case of hexamethonium, but we must insist on the susceptibility and unpredictable response of each patient. In general, after a period of adaptation of some weeks the maintenance dose stabilizes itself at a level which remains fairly constant.

The patient is always informed of possible secondary effects of Ansolsen and how to correct them. As regards orthostatic hypotension manifested by amblyopia, dizziness and sensation of weakness, it is sufficient to advise the patient either to sit or if necessary lie down. Should these effects persist up until the time of the next dose, which is very rare, the dose should not be taken, and if these phenomena reappear too often the physician must modify the dosage. The patient must also be careful not to let himself become constipated, and he should be warned not to let 48 hours pass without a bowel movement. Various laxatives, pref-

erably mineral oil, cascara or milk of magnesia, are recommended in doses sufficient to provide a daily bowel movement. After two or three days of constipation, the patient should be given an enema; and in cases of obstinate constipation going beyond four days, it is preferable to suspend the medicament for a day and to administer intramuscularly 1 to 2 0.25-mg. ampoules of Prostigmine followed in $\frac{1}{2}$ to 1 hour by an oil-soap enema (aa). Other secondary effects are never serious enough to justify other than symptomatic treatment.

(c) Association of Drugs

Several authors have already mentioned the advantages of Ansolsen in association with other hypotensive agents such as rauwolfia.^{12, 13} Maintenance doses with these combinations are said to be lower, secondary effects less severe, and fluctuations of arterial pressure less marked.

We have had occasion to use combinations of Ansolsen with rauwolfia and of Ansolsen with Apresoline. In addition, in two cases we have used successively, Ansolsen alone, then associated with Apresoline, and afterwards with Apresoline and rauwolfia. The most noteworthy observation has been not so much the fall as the decrease in maximal and minimal excursions of arterial pressure.

(c) Contraindications

Ansolsen should not be used in cases of advanced arteriosclerosis, or in cases where patients have already suffered from cerebral or cardiovascular accidents. It should not be used in patients whose entire co-operation is not assured, or in those unable to visit the doctor regularly. One case illustrates well the hazards of this medication.

F.G. appeared at the hospital complaining of headaches and decrease of vision that had been present for several years. Examination showed an arterial pressure of 280/110 mm. Hg with a marked decrease in renal function and a great increase in cardiac volume. This patient, in addition, showed signs of very advanced arteriosclerosis. After several days of observation, treatment with Ansolsen was instituted according to the method indicated above, the patient being hospitalized and under strict surveillance. Gradually a dose of 600 mg. per day was reached without appreciable results; then suddenly, at noon, about 1 hour after taking his medicine, the patient felt dizzy on getting up. His arterial pressure, taken immediately, was 140/88 mm. Hg. He was immediately put back to bed and the pressure rapidly regained its former level. Despite all possible care, he soon vomited copiously, faded gradually into unconsciousness and died seven days later. Autopsy showed an extremely advanced atherosclerosis of all

large and medium-sized arteries, particularly the cerebral vessels, with softening of two cerebellar lobes and thrombosis of cerebellar arteries.

RAPID CONTROL OF ARTERIAL PRESSURE

When rapid control of pressure is required, Ansolsen is the drug of choice and it can be administered intramuscularly, alone or in association with a retarding substance (polyvinylpyrrolidone) to delay absorption. The dose varies from 5 to 15 mg. by the subcutaneous route. It is always wise first to give a trial dose of from 2-3 mg. to test the susceptibility of the subject and avoid pressure falls either too great or too sudden in particularly sensitive patients.

Generally a lowering of pressure is obtained which is often spectacular (Fig. 5), with almost immediate relief of the patient's symptoms.

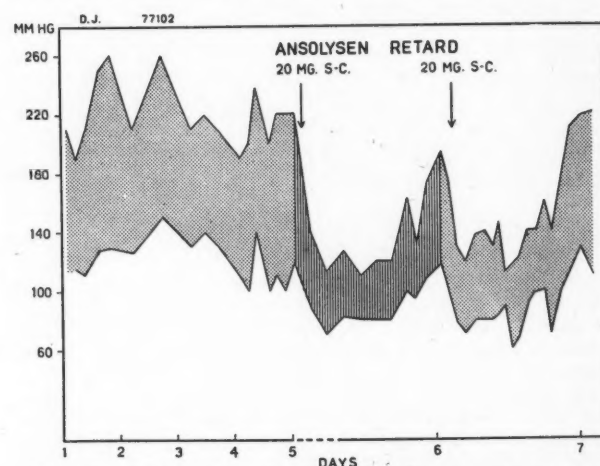


Fig. 5.—Spectacular effect of Ansolsen administered parenterally. Mrs. D.J., with severe essential hypertension, had two subcutaneous injections of Ansolsen retarding solution with an interval of 24 hours. The important role of this drug in all cases where a rapid reduction of arterial pressure is necessary is demonstrated.

CONCLUSIONS

We have studied the action of Ansolsen alone, or in association with other hypotensive agents, in 22 subjects with essential hypertension, and in 8 cases of malignant hypertension.

Ansolsen is a powerful hypotensive drug giving relief in the great majority of cases. It is preferable to use it in association with Apresoline with or without addition of rauwolfia, in order to diminish extreme fluctuations of pressure, while at the same time lowering the doses normally required of each medicament.

Ansolsen should not be employed except with the greatest care. Its use is governed by certain specific indications, such as cases of essential hypertension, either severe or malignant, which are resistant to Apresoline or rauwolfia.

The authors wish to express their gratitude to Miss Fernande Salvail and Miss Lucette Salvail for their helpful collaboration.

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RÉSUMÉ

Un des dérivés organiques des composés quaternaires d'ammonium est le bitartrate de pentaméthylène:1-5-

bis-(1-méthylpyrrolidinium) connu sous le nom commercial de Ansolysen. Comme l'hexaméthonium, il agit par blocage de la transmission nerveuse au niveau des ganglions autonomes. Les effets secondaires sont les mêmes. Ce médicament fut employé par les auteurs dans une série de 30 hypertendus, dont 8 avaient une hypertension maligne. L'observation s'étendit sur une période variant de 4 à 56 semaines.

Une chute de tension artérielle, quelquefois marquée, fut observée dans chaque cas. L'effet fut encore plus considérable lorsque le médicament avait été employé en combinaison avec la rauwolfia. On observa une régression importante des lésions oculaires. L'hypertrophie ventriculaire gauche ne fut cependant pas améliorée.

La dose initiale du traitement était de 20 à 40 mg. administrée entre 15 et 20 minutes avant chaque repas et au coucher. Chaque dose fut augmentée de 20 à 40 mg., quatre fois par jour, à des intervalles de 5 à 7 jours jusqu'à ce que l'effet hypotensif fut obtenu. La dose habituelle varie entre 160 et 800 mg. par jour. Les mêmes précautions vis-à-vis l'hypotension orthostatique doivent être observées comme dans l'emploi des autres hypotenseurs. Il en va de même pour les contre-indications.

Quand un abaissement rapide de la tension artérielle s'impose, Ansolysen peut être administré par voie intramusculaire ou sous-cutanée à raison de 5 à 15 mg. Il est toujours prudent de commencer avec 2 ou 3 mg. afin d'évaluer la sensibilité individuelle du malade au médicament.

M.R.D.

THE CHANGING PATTERN OF NEUROSYPHILIS*

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IT IS FIFTY YEARS since Schaudinn and Hoffmann recognized that the *Spirochæta pallida* was the causative agent of syphilis. During this half century, the picture of neurosyphilis has undergone dramatic change. The first important trend occurred 46 years ago with the introduction by Ehrlich in 1910 of specific therapy in the form of the arsenical compound "606". This was followed by a succession of new arsenicals and bismuth. Fever therapy, although known and tried for many years, was not in common use until about 1917. The climax occurred with the introduction of penicillin in the therapy of syphilis, just about 10 years ago.

Proof that syphilis in general and neurosyphilis are being successfully combated can be readily obtained by reviewing the incidence of these cases in the special treatment clinic of the Toronto General Hospital. In 1940, 1,088 cases

were under treatment for syphilis, of which 373 were newly diagnosed during the year. In 1949 there were 598 cases under treatment, and only 158 newly diagnosed; in 1954 there were 341 cases, 72 newly diagnosed. Among these, there were 13 new patients with neurosyphilis. Although previous annual figures relating to neurosyphilis are not available, it has generally been considered that 5% to 10% of all patients with syphilis show neurological involvement if they are not treated or are inadequately treated.

In the past four years, 180 cases of syphilis with some form of neurological involvement have been reviewed. This figure represents the sum total of all patients with neurosyphilis who have attended the special treatment clinic of the Toronto General Hospital during that period. This group does not include all the cases of neurosyphilis treated or recognized throughout the hospital in recent years, but it does represent a large proportion of them. Many were treated both as inpatients and outpatients. This study includes 177 cases personally reviewed. Most patients were observed on several occasions. The three not included were eliminated primarily because of insufficient data.

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It is not my purpose to review the well-known classical forms of neurosyphilis, for it is apparent that the day for this variety of original observation of advanced forms of neurosyphilis is long since past, in view of the apparent changes following upon the introduction of specific therapy. The detailed and vivid descriptions of authors such as Kinnier Wilson¹ will likely never be surpassed. In effect, for the most part we are seeing abortive or relatively incomplete forms of neurolues. We still occasionally encounter some far-advanced and classical patterns, but these represent relics of a previous phase in therapy, still within our midst.

Some of the problems or questions that might be solved or answered by a current study of neurosyphilis include the following:

1. The relative incidence and varieties of neurosyphilis.
2. The general pattern and course of neurosyphilis in the pre-penicillin and post-penicillin eras. This would include the clinical picture as well as serological and spinal fluid changes.
3. The question whether neurosyphilis may progress in a clinical form in spite of inactivity of the cerebrospinal fluid following therapy.
4. The relationship of previous therapy to the development of neurosyphilis.
5. The problem of resistant forms or cases difficult to control, including the problem of relapse, as determined by either the clinical pattern or by spinal fluid examination.
6. The necessity for other forms of specific therapy in addition to penicillin.
7. The occurrence of the so-called Herxheimer reaction with commencement of therapy.
8. The effect of penicillin on some of the particular manifestations of neurosyphilis, including lightning pains, gastric crises, and the development of Charcot joints.
9. General observation of interesting and unusual cases of neurosyphilis, as well as the association of several other features, such as syphilitic cardiac disease or peptic ulcer.
10. The effect of treatment on the pathological changes associated with syphilis.

Some of these questions can be answered directly from our study. Others have already been the subject of intensive review, and have brought forth substantial conclusions, some of which are still controversial.

Of the 177 cases of neurosyphilis in this review, many were of long duration, and still

under observation because of some evidence of clinical progression or activity in the cerebrospinal fluid within recent years. However, a large percentage had only recently been recognized as having neurological complications of syphilis, found either upon routine examination of the cerebrospinal fluid in the course of treatment, or by the various clinical manifestations. This group included 150 males and 27 females.

Classification of all cases was not always clear-cut, for it is well recognized that there is a considerable amount of overlapping in the clinical as well as in the pathological picture. However, in attempting to assess each case as accurately as possible, the following distribution was arrived at:

Tabes dorsalis—56.

Asymptomatic—43. This includes patients with spinal fluid changes only, and no symptoms or signs of syphilis.

General paresis of the insane—32.

Meningovascular (cerebrospinal)—17. This group includes primary involvement of the meninges or blood vessels, of either the brain or spinal cord.

Pupillary involvement only—14.

Taboparesis—a combination of tabes dorsalis and general paresis—4.

Absence of ankle jerks only—4.

Optic atrophy only—4.

Congenital neurosyphilis—3. Two of these were primarily paretics, and one patient had epilepsy with mental retardation.

The monosymptomatic groups have been purposely left separate, in preference to attempting to force them into any of the above specific classifications. This was done primarily because of the conflicting opinions regarding the outcome of these cases. In general, in patients with pupillary changes only, the condition may remain essentially stationary or they may develop tabes dorsalis, or general paresis, or even meningovascular neurosyphilis. Similarly in the group with optic nerve involvement exclusively, the condition may remain stationary, or the full syndrome of tabes dorsalis may develop. Some examples of patients with pupillary changes bearing resemblance to Argyll-Robertson pupils in conjunction with absent ankle jerks have been found, and these are included in the group of tabes dorsalis. They appear to represent a *forme fruste* of tabes dorsalis, which was recognized even before penicillin therapy.

There were several particularly interesting clinical patterns, including two examples of neurosyphilis in association with Parkinsonism. One of these occurred in a patient now known to have had carbon monoxide poisoning. It is likely that the Parkinsonism is best accounted for on this basis. The other was an example of a well-developed Parkinsonism in a 55-year-old man who had tabes dorsalis of many years' duration, with inactive cerebrospinal fluid, before the actual development of the features of basal ganglia involvement. The patient had previously received penicillin. The question in this case is whether the Parkinsonism is of syphilitic origin or whether its occurrence is purely coincidental. We are inclined to favour the latter view.

There was one example of tabes dorsalis with early luetic amyotrophy of the shoulder girdles. One other patient had neurosyphilis and associated motor neurone disease which was rapidly progressing. The relationship to the luetic process here is not definitely determined.

In seven patients neurosyphilis was associated with cardiac involvement and evidence of aortic insufficiency. There were three examples of peptic ulcer occurring in tabetics. Each of these had presented with a picture resembling gastric crises. This is a well-recognized association, and suggests some neurogenic influence in the production of gastric ulcer in such cases. The lesion has been attributed to a vagus nerve disturbance. In one of our patients a vagotomy was performed, and on later examination although the ulcer was healed the pattern of persistent gastric crises remained essentially unchanged. Two of these patients appeared to have true gastric crises as well as the peptic ulcer. From the evidence of the operative case, one would conclude that the so-called vagus neuritis suggested as one of the many theories to account for gastric crises is not the only causative factor.

Penicillin therapy appears to have altered the general picture of neurosyphilis. The incidence of monosymptomatic cases and so-called *formes frustes* of the various clinical patterns seems to be increasing. Many of these cases appeared before the penicillin era, but even during therapy, which frequently extended over several years, new signs and symptoms seemed to develop. With penicillin, the condition appears to remain fairly stationary in most cases and upon occasion it showed improvement, which con-

tinued for many months. There are several examples of patients treated extensively in the pre-penicillin era, in whom arsenicals, bismuth, mercury and fever, often in combination, failed to avert the progression of the clinical picture. Some of these showed either continued activity or reactivity in the cerebrospinal fluid. This was particularly indicated by a high cell count, as well as a high protein level, very strongly positive Wassermann or Kahn reaction, and abnormal colloidal gold curves.

There are some striking examples in this series, where after years of continued activity in the cerebrospinal fluid in spite of the persistent use of the early forms of therapy, a course of penicillin sometimes returned the active contents to normal within a few months. Following Dattner's² observations we have also been inclined to regard the cerebrospinal fluid changes as the most reliable indication of activity in the nervous system. In this connection it is well known that neurosyphilis may continue to progress clinically in spite of inactivity of the cerebrospinal fluid, either spontaneously or after therapy. This may be accounted for on the basis of continuation of the reactive or destructive process set up in the nerve tissue or supporting tissues, in spite of inactivation of the spirochæte itself. One can readily conceive of the continuation of the end results of nerve degeneration which has passed beyond a stage of recovery before treatment. This is well demonstrated in certain cases of general paresis of the insane which may continue to progress clinically in spite of treatment.

Tabes dorsalis may also show clinical progression in the form of development of Charcot joints, and by the persistence or increased severity of gastric crises or lightning pains. Further examples are those of progressive deafness and sometimes progressive amyotrophy.

From this it would appear that precise evaluation of the effects of therapy are linked with the sensitive components of the cerebrospinal fluid. These in particular are the cell count and to some extent the total protein estimation. These elements rapidly return to normal after penicillin therapy. The process usually takes several weeks for the cell count, and generally there is a considerable variation with regard to the protein. A continued high cell count indicates a resistant case. A high protein level is sometimes indicative of this, but not so definitely, for upon

occasion the level may remain high for several years without further evidence of activity. The colloidal gold and Wassermann tests of the spinal fluid are unreliable indices of activity. Persistently high titres and grossly abnormal curves have been seen for years in spite of clinical improvement after treatment. A change from a normal to an abnormal curve, or a weakly positive to a persistent strongly positive cerebrospinal Wassermann reaction is of significance, but this is generally accompanied by a change in the cell count and protein level as well. After penicillin therapy, the general trend is for the various elements of the cerebrospinal fluid to return to normal. This reversal may never be complete, however. The evidence tends to suggest that arsenicals, bismuth, and fever quite frequently inactivate the cerebrospinal fluid, but there were many exceptions and, as mentioned above, there were several examples of relapsing or resistant cases after years of continued therapy. These cases all seemed to be permanently controlled by penicillin.

In addition, there were frequent examples of persistently positive spinal fluid Wassermann reactions and abnormal colloidal gold curves, which had not been affected by earlier therapy, and soon showed a trend of either partial or complete return to normal after penicillin.

In a few cases treated with penicillin, relapses occurred. One patient showed a relapse as evidenced by cerebrospinal fluid activity and headache, two years after penicillin therapy. Another patient relapsed after three years. In each case one or two additional courses of penicillin were necessary to inactivate the cerebrospinal fluid completely, and no further recurrence was apparent. One patient had 16,000,000 units of penicillin initially, but required 30,000,000 before activity subsided. Dattner³ had previously concluded that, if cerebrospinal fluid was inactive two years after penicillin therapy, there was no chance of a relapse. Our results bear this out in all but one instance, when the interval was three years. However, we have no precise information on the cerebrospinal fluid picture between the first and third years. Further penicillin was given to this patient, and four years afterwards the pattern was that of complete arrest, both from the clinical standpoint and from the cerebrospinal fluid examination. In no case did penicillin in either single or multiple courses fail to inactivate the cerebro-

spinal fluid. There is only one example in our series of a patient's receiving close to adequate amounts of penicillin in the early stages of syphilis and subsequently developing evidence of neurological involvement. This was a 26-year-old man treated in 1946 for a primary sore. At that time he received 3,000,000 units of penicillin in addition to arsenicals and bismuth in small quantities. Six months later the cerebrospinal fluid was entirely negative. A rising titre in the Kahn reaction in the blood was noted, and the patient received further arsenicals and bismuth for two years. In 1950 the cerebrospinal fluid was very active and all elements returned to normal in six months after 15,000,000 units of penicillin had been given. No clinical signs were present at any time. This patient has been well and spinal fluid has been inactive for four years. It appears that the initial treatment with 3,000,000 units of penicillin was inadequate. Actually, our earlier syphilis cases are treated with a minimum of 3,500,000-4,000,000 units of penicillin initially. The infrequency of such a relapse is in striking contrast to the former situation in which, even after 150 or more injections of arsenic and bismuth over three years or longer, in addition to fever in some cases, cerebrospinal fluid activity would occur, often in conjunction with clinical features of active neurosyphilis.

It has been repeatedly shown that if the cerebrospinal fluid is inactive in cases of general paresis as well as other examples of neurosyphilis, no further benefit can be gained by giving repeated courses of penicillin to prevent clinical progression. There are several examples in our series of progression of paresis with inactive cerebrospinal fluid. Some eventually were committed to Ontario Hospitals in spite of repeated courses of penicillin during the period of clinical progression. The reason for this has been discussed earlier in the paper; it is related to the irreversible change involving the nerve tissue. We no longer find it necessary to use mercury, bismuth or arsenicals in the treatment of syphilis in the early or tertiary stages. Penicillin alone seems to be adequate, as indicated in our series of patients as well as by several comprehensive reports in the literature.⁴⁻⁶ Fever therapy has not been used in our clinic for the past four years. Convincing controlled studies have tended to eliminate this form of therapy, and it is rapidly being abandoned in widespread

fashion, although some centres still use fever as a last resort in severe and progressive cases of general paresis of the insane.

The Herxheimer reaction has scarcely been a problem in our patients. At one time it was felt that bismuth therapy should precede penicillin therapy. It was also considered best to give penicillin in small quantities initially, and gradually increase the dosage to therapeutic levels in order to avoid a Herxheimer reaction. This precaution was followed initially in our cases but was later abandoned. Serious Herxheimer reactions have not occurred in spite of the fact that large quantities of penicillin were given initially to very active cases in our series. Other studies⁷ have shown that small amounts of penicillin, gradually increased, do not in any event prevent the Herxheimer response.

Although occasional deaths have been reported,⁸ which have been attributed to Herxheimer reactions even after small quantities of penicillin, we have not found this to be a problem in therapy, and few significant untoward results have been observed. There has been an occasional mild and transient increase in mental deterioration, and slight febrile reaction. Some reactions undoubtedly have been overlooked because the patients were treated as outpatients. We know of two severe Herxheimer reactions that occurred during penicillin treatment in hospital recently, but these patients were not in the series reviewed. One other patient with severe paresis continued to deteriorate rapidly and followed a downward course for three weeks which eventually led to death. This occurred before and during the course of penicillin therapy. It is considered unlikely that there was any relationship to a Herxheimer pattern, for this febrile reaction did not commence until one week after penicillin therapy began, and rapid deterioration was apparent even before the first treatment. This case could rightly be classified as a rapidly developing destructive variety of general paresis, beyond the stage responsive to therapy. There have been several minor reactions, and one severe reaction attributable to penicillin sensitivity itself.

The problem of lightning pains still remains unsolved. They have generally been attributed to the process of destruction and irritation of the posterior root near the root entry zone of the spinal cord. There is essentially a radicular perineuritis. These pains have been notorious for persisting after all forms of therapy; in spite of

successful control of the course of the disease, as well as inactivation of the cerebrospinal fluid. We observed six patients in whom penicillin seemed to have a definite and beneficial effect on lightning pains. Some of these cases relapsed after a period of several months, however. One patient stated that for the first time in 25 years he had relief from pain, and this occurred immediately after the first injection of penicillin. There was no recurrence in the six months that he remained under our observation. On the other hand, there was a larger group of patients in whom lightning pains were in no way affected by penicillin therapy. In two cases lightning pains developed for the first time during the actual course of penicillin treatment. Another patient complained of these pains one year after penicillin therapy had been given. In general, there is a variable pattern of response, and the evidence would suggest that in possibly 40% of the cases some improvement does occur with relief of lightning pains after penicillin therapy, although the improvement is often short-lived.

Similarly, gastric crises are not generally affected by penicillin, although an occasional example suggested that there was some definite effect. In general one could not be impressed with the results, as close scrutiny indicated that there had been spontaneous remissions previously, and this pattern could readily have accounted for the improvement in the cases in question. Actually, two out of four patients seemed temporarily improved.

The fact that lightning pains and gastric crises may develop in patients who have received apparently adequate treatment, and in whom the cerebrospinal fluid has shown no evidence of activity, is well shown in some of our patients, and has been mentioned earlier. Another interesting example of progression of syphilis in spite of negative spinal fluid is illustrated by a patient who began to have evidence of multiple Charcot joints and spontaneous fractures six years after the cerebrospinal fluid had been inactivated. The fractures occurred spontaneously in several different locations. There was only minimal evidence of demineralization of the bones and no indication of change in the significant biochemical studies. Spontaneous fractures in tabetics have been previously recognized, but are generally considered extremely rare. They have been attributed to trophic changes resulting from involvement of the lateral horn of grey

matter in the spinal cord. The patient in question had not been treated with penicillin in the past.

From the pathological standpoint, we have previously seen examples of arrested general paresis and other forms of neurosyphilis after treatment with arsenicals and fever. In these cases there is essentially evidence of a healed and inactive process. This pattern seems to be becoming more frequent since the introduction of penicillin. The earlier the treatment is given, the more normal the tissue appears to be. This is particularly striking in cases of general paresis, and fairly dramatic examples of clinical improvement with penicillin would seem to fit well with the pathological evidence of an essentially healed process. Our own observations on some of the pathological material available have not actually included examples in which penicillin alone has been given, hence no conclusion can be drawn from that standpoint.

In general, it may be stated that no treatment known is designed to restore degenerate or narcotic parenchyma, nor can therapy attempt to overcome the advanced processes of tissue reaction. Hence treatment is primarily aimed at preventing further damage. There may be some restoration in function in tissue only partially damaged. On the other hand, as we have already implied, some form of destructive or irritative lesion may persist as a result of a process that had begun long before therapy itself had been effective.

The general routine for penicillin treatment has been that of intramuscular injections of 600,000 units of procaine penicillin G in oil (aluminium monostearate) three times weekly for about four to six weeks. In cases of neurosyphilis there is no absolute rule, but generally 7,000,000-11,000,000 units of penicillin have effectively controlled the large majority of cases, and active spinal fluid has returned to normal. When repeated courses are necessary, about 15,000,000 units are given with treatment extended over a period of eight weeks.

In addition to the pattern of cerebrospinal fluid changes, the general quantitative titres of the blood reaction are also carefully observed. No patient treated for early syphilis is discharged even after adequate therapy, unless blood titres have remained low for a minimum of three years, and a spinal fluid examination three years after therapy has shown no evidence of activity. In this way, it should be possible to

recognize and control effectively with penicillin all cases of early syphilis, and to prevent the late complications, including neurosyphilis.

SUMMARY AND CONCLUSIONS

1. A review of 177 patients with neurosyphilis has been given. Penicillin alone was the chief therapeutic measure used, although other forms of therapy had been given to many of the patients in the past.
2. Some interesting examples of neurosyphilis have been described.
3. The general trends in the clinical pattern and cerebrospinal fluid pattern after therapy before and during the penicillin era have been discussed.
4. The effectiveness of penicillin alone in the treatment of neurosyphilis has been emphasized.
5. The relative effect of penicillin therapy on gastric crises, lightning pains, and Charcot joints, as well as on advanced paresis, has also been discussed.
6. Penicillin alone has been effective in controlling all groups of neurosyphilis. In general it has been least effective in altering the course of advanced paresis, or moderately advanced tabes, when fixed and irreversible reactions have already occurred.
7. A general program for the effective control and elimination of neurosyphilis has been briefly outlined.

Dr. R. Smith and Dr. H. H. Hyland have offered some valuable suggestions in the preparation of this paper.

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WHY DIDN'T THEY ASK?

"I was once asked to see a girl with dermatitis artefacts with the idea of hypnotizing her and finding out what she was doing to her skin, and why she was doing it. Before considering hypnosis I said to her: 'Tell me; are you putting something on your skin which makes all those sore places?' She replied: 'Well, yes; I do it with hydrochloric acid from my brother's laboratory; you see, if my Dad thinks I'm ill he treats me much more nice.' The consultant, when I told him the solution, was most impressed until I explained the method of obtaining it. He admitted that it had not occurred to him."—Richard Asher, *Brit. M. J.*, 1: 313, 1956.

Case Reports

KAPOSI'S SARCOMA*

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EIGHTY-THREE YEARS have elapsed since the first description of this disease was published, in 1872, by Kaposi¹ under the name of "idiopathic multiple-pigmented sarcoma". Numerous new names have been proposed, as reported by Choisser and Ramsey,² but the terms Kaposi's sarcoma and multiple idiopathic hæmorrhagic sarcoma are still widely accepted and used in the medical literature.

Kaposi's sarcoma is relatively rare, fewer than 700 cases having been published to date. Most patients originate from Russia, Poland and Northern Italy. According to Dörffel,³ the distribution of the disease is geographical rather than racial, although this condition is extremely prevalent among the Jewish and Italian races. Kaposi's sarcoma is almost exclusively seen in males (95%). The largest number of patients are between 40 and 80 years old. The condition is seen most frequently in labourers, and patients whose occupation keeps them on their feet for long intervals.

The sites of choice of Kaposi's sarcoma (73% of cases) are the feet and legs, but it may also involve almost every organ of the body. The gastrointestinal tract, the liver, the lungs, the lymph nodes and the osseous system are the internal structures most frequently involved. Choisser and Ramsey² and Tedeschi *et al.*⁴ reported cases without skin involvement.

The duration of the disease varies from eight months to 25 years.

Many hypotheses have been suggested to try to explain the histogenesis of Kaposi's sarcoma. Kaposi interpreted it as a cutaneous sarcoma affecting the blood vessels. Other authors have considered it as a true blastoma, or as an infectious granuloma, or as a disease originating from nerve tissue⁵ or the reticulo-endothelial system.

Dörffel states, after reviewing 372 cases including 16 personal cases, that "the sarcoma of

Kaposi is a disease of the reticulo-endothelial system, which disease is 'a priori' not a true blastoma, but which may become one in some cases after long continued irritation." Cuccione,⁶ Greppi and Bettoni,⁷ Goldsmith,⁸ McCarthy and Pack,⁹ Jausion and his colleagues,¹⁰ and Stich *et al.*¹¹ also favour the Dörffel hypothesis. Other authors, among them MacKee and Cipollaro,¹² Choisser and Ramsey, consider that the disease is truly neoplastic.

The concomitant occurrence of Kaposi's sarcoma with Hodgkin's disease,¹³ or leukæmia,¹⁴⁻¹⁷ or mycosis fungoides,^{18, 19} has been reported. Lever²⁰ believes that there are too few cases and insufficient proof to relate Kaposi's sarcoma and lymphomas. Allen²¹ is convinced that a more than coincidental relationship exists between Kaposi's sarcoma and the several malignant lymphomas.

The association of Kaposi's sarcoma and diabetes mellitus has been reported by Hurlbut and Lincoln,²² who found evidence of diabetes mellitus in 6 of a series of 13 patients suffering from Kaposi's sarcoma. Ronchese and Kern²³ reviewed 16 cases and found no diabetes mellitus among them. They suggest that the high incidence of diabetes mellitus seen by the previous authors is due to the preponderance of Jewish patients (10 of 13) in their series.

The present case was one of a Kaposi sarcoma occurring in a Canadian of French origin. The absence of any published case of Kaposi's sarcoma in the Canadian medical literature and the great interest in this disease seemed to us good reason to report it.

E.R., a 55-year-old French Canadian man, was admitted to the Hôtel-Dieu Hospital of Quebec, on December 5, 1953, complaining of a painful new growth under his right foot, of 19 months' duration. Seven months previously, he had been operated on in another hospital, but the lesion had recurred.

The family and past history did not reveal anything special. He was a first-class engineer, and was on his feet for long periods.

On examination, there was on the right plantar region, near the heel, an apple-sized tumour about two inches (5 cm.) in diameter. The surface was purplish red and had an angiomatous appearance (Fig. 1). Blood and pus were oozing out in some areas. No other lesion was present on the skin, except three tiny bluish macules located on the left plantar region, the external aspect of the left leg and the dorsal aspect of the left wrist. In the right inguinal region, a few hard, mobile and enlarged lymph nodes were palpable. Physical examination otherwise was negative.

Laboratory studies were reported as follows: The hæmoglobin value was 12 g.; red cell count 4,000,000 and white cell count 12,200, of which 74% were polymorphonuclear leukocytes, 21% lymphocytes and 5% monocytes (Table I). The urine and the Wassermann

*From the Dermatology Service of L'Hôtel-Dieu de Québec Hospital. Paper read at the Ninth Annual Meeting of the Canadian Dermatological Association held in Niagara Falls, Ont., in June 1955.

TABLE I.

BLOOD COUNT AT SUCCESSIVE ADMISSIONS								
	Red cell count	Hb. (grams)	White cell count	Neutrophils	Eosinophils	Basophils	Lymphocytes	Monocytes
Dec. 1953	4,000,000	12.0	12,200	57%	2%	15%	21%	5%
Nov. 1954	3,020,000	6.6	17,600	70%	2%	16%	5%	7%
June 1955	4,390,000	11.2	12,700	73%	1%	0%	18%	8%

reaction were normal. Blood urea level was 0.04 g. %.

A radiograph of the right foot showed a tumour of soft tissues in the region of the os calcis (Fig. 2). A radiograph of the heart and lungs was normal.

A biopsy of the tumour of the right foot showed a tumour-like lesion which had ulcerated the epidermis. Beneath the ulceration there was an area of angiomatous proliferation made up of capillaries with swollen endothelial cells and generally an outer layer of perithelial cells. These capillaries were embedded in a loose connective tissue. Deeper, there was a dense cellular proliferation made up of strands of plump fibroblasts showing fairly numerous mitoses. In this area collagen was scarce but there existed large foci of extravasated erythrocytes and haemosiderin granules (Figs. 3 and 4).

Diagnosis.—Kaposi's sarcoma.

A biopsy of the right inguinal node showed a subacute adenitis without trace of neoplasm.

The diagnosis of Kaposi's sarcoma having been well established, the following treatment was instituted: potassium permanganate wet dressings, 400,000 units of penicillin daily for a total dose of 6,000,000 units and x-ray therapy. The patient received 2,100 r., divided in 14 treatments of 150 r. (at 200 kV and 6 mA; Fil.: 0.5 co. Dist.: 50, T.: 7' 30"). On January 5, 1954, he was discharged from the hospital. Thirteen days later there was almost no change, but on February 15 the improvement was evaluated at more than 50%. On March 29, the healing of the tumour was almost complete, but there was a new purplish-red nodule on the external aspect of the right foot. X-ray therapy was recommended for the new lesion.

The patient was not seen until the end of October, at which time hospitalization was advised because of recurrence of the tumour.

On admission, on November 19, 1954, a large purplish red tumour covered almost half of the right plantar region and there was also a smaller one on the lateral aspect of the same foot (Fig. 5). The three tiny bluish macules noticed in December 1953 were unchanged.



Fig. 1.—(Above).

Fig. 2.—(Below).

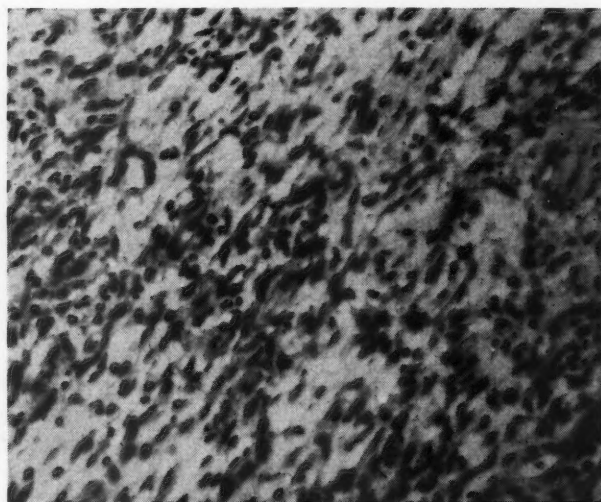


Fig. 3

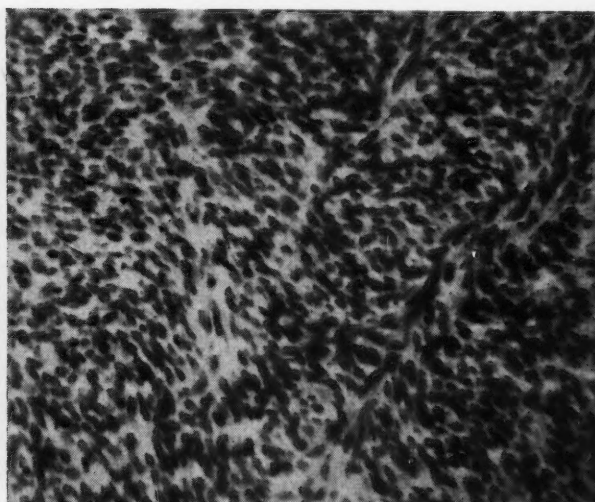


Fig. 4



Fig. 5



Fig. 6

The patient was complaining of loss of blood from the tumours, and of digestive troubles simulating a gastric ulcer.

Laboratory studies were reported as follows: Hb 6.6 g.; red cell count 3,020,000, and white cells 17,600 of which 88% were polymorphonuclear leukocytes, 5% lymphocytes and 7% monocytes (Table I). The urine and Wassermann reaction were normal. The sedimentation rate was 77 mm. in one hour and 115 mm. in two hours. A myelogram showed a hyperplastic bone marrow with 1% of plasmocytes.

Radiography of the right foot showed that the tumour of the soft tissues was larger than in December 1953. There was also a bone erosion and condensation at the external end of the tibia and fibula, suggestive of bone metastases (Fig. 6).

Heart, lungs and oesophagus were radioscopically normal. A gastrointestinal series demonstrated a huge ulcer crater high on the small curvature of the stomach (Fig. 7). The duodenal bulb and loop were normal.

During this second hospitalization, the treatment consisted of routine gastric ulcer diet, a blood transfusion



Fig. 7

of 480 c.c., 10,000,000 units of penicillin (1,000,000 daily) and x-ray therapy to a total dose of 3,000 r. (10 sessions of 300 r.).

Before his discharge from hospital, on December 18, 1954, the patient was advised to have an amputation of his right leg, but he refused categorically.

He was not seen before June 7, 1955, and this at our repeated request. At this last date, on examination, there was a large flat-topped purplish-red tumour in the right plantar region (Fig. 8). A slight blood oozing was present. On the right external aspect of the foot, a small bean-sized reddish-purple nodule was seen. All these skin lesions were much less pronounced than five months previously.

The increase in size of the right ankle showed a more active process in the lower ends of the leg bones. Right inguinal lymph nodes were still palpable. The three tiny bluish

macules had not increased in size, but a biopsy of the one on the dorsal surface of the left wrist was recommended.*

Radiography showed that the soft tissue mass under the foot had decreased, but the bone density had increased. Metastases, as described before, were noted at the ankle, with extension to the diaphysis of the tibia (Fig. 9).

The blood count was practically normal except for 12,700 white cells and 8% monocytes (Table I).

The patient stated that he was able to resume his work for a month, but increased pain in his foot and leg forced him to stop.

He had not suffered from his stomach since his last hospitalization five months previously.

A new attempt to persuade him to have his leg amputated was unsuccessful.

COMMENTS

Kaposi's sarcoma must be a rare disease in Canada because, as far as we know, this is the

*The biopsy specimen proved to be a blue naevus.



Fig. 8



Fig. 9

first case reported in a Canadian of French origin.

Because Kaposi's sarcoma is mostly prevalent among the Jewish and Italian races, we made a family inquiry, but were unable to trace any other race mixture in his parents and grandparents, who were born in and lived in Canada.

Our patient is suffering from Kaposi's sarcoma with lesions located in the skin, the bones and possibly the stomach. Bone lesions have been frequently reported in the European literature, but rarely in the English literature according to Ronchese and Kern.²⁴ The acute gastric ulcer episode in this case has not definitely been proved to be an ulcerated Kaposi lesion, but in view of the frequent involvement of the gastrointestinal tract by this disease, we assume that we are dealing with such a lesion.

We agree with authors who favour a multicentric origin rather than a metastatic origin of lesions in Kaposi's sarcoma.

Hæmograms on his second hospitalization showed an anæmia with about 3 million red cells and 6.6 g. of hæmoglobin. This anæmia is interpreted as secondary to frequent and abundant bleeding from the sarcomatous lesions. The white cell count varied between 12,200 and 17,600. While this is not characteristic of Kaposi's sarcoma, Dörffel reported a definite leukocytosis in many cases. A normal eosinophilia of 1 and 2% was found, but the monocytosis varied from 5 to 8%. Vigne²⁵ and Lortat-Jacob,²⁶ among other authors, consider a monocytosis of 5 to 9% as a frequent finding in Kaposi's sarcoma. As reported by Stats,²⁷ an active hyperplastic bone marrow was found in our patient.

X-ray therapy is unanimously recognized as effective in the treatment of Kaposi's sarcoma. Unfortunately it is followed in most cases by recurrence of the lesions. Our patient received radiotherapy in two instances and only temporary remissions were obtained. Penicillin was associated with the radiotherapy on account of reports^{28, 29} of its value in Kaposi's sarcoma. Our impression is that penicillin has no effect on the sarcomatous lesions themselves, but may help to control the secondary infection.

The fact that Kaposi's sarcoma is a rare disease in women has suggested the treatment of this disease with oestrogenic hormones, but no practical result was obtained by a few authors who used oestrogenic hormones and also cortisone and corticotrophin (ACTH).

CONCLUSIONS

Kaposi's sarcoma is a rare disease, and there is no unanimity of opinion regarding its histogenesis and etiology.

A case of this disease, occurring in a Canadian of French origin, is reported. The sarcomatous lesions were localized in the skin, bones and presumably the stomach. A moderate leukocytosis and 5 to 8% of monocytes were observed.

X-ray therapy induced temporary remissions, but penicillin seemed ineffective.

Our patient was admitted to the Orthopædic Service of Dr. Louis Philippe Roy, to whom we are indebted.

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ANATOMICAL APPROACH TO STUDY OF SMOKING AND BRONCHOGENIC CARCINOMA

O. Auerbach et al. (*Cancer*, 9: 76, 1956) report that basal cell hyperplasia, and to a lesser degree stratification and squamous metaplasia, distinguishes the epithelium of the bronchial tree of male smokers from that of male non-smokers. In this series of 41 persons all bronchogenic cancers studied (14) were in moderate or heavy smokers, and all such cancers that were discarded from the study because of technical difficulties were from patients with histories of smoking.

OBSTRUCTIVE ULCERATED ENDOMETRIOSIS OF THE RECTUM DIAGNOSED BY PROCTOSCOPIC BIOPSY*

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OBSTRUCTIVE ENDOMETRIOSIS of the rectum is not uncommon. We have been unable, however, to find any reference to ulceration of the rectal mucous membrane by endometrial tissue. We wish to report an instance in which the definitive diagnosis of obstructive endometriosis of the rectum was established first by proctoscopic biopsy.

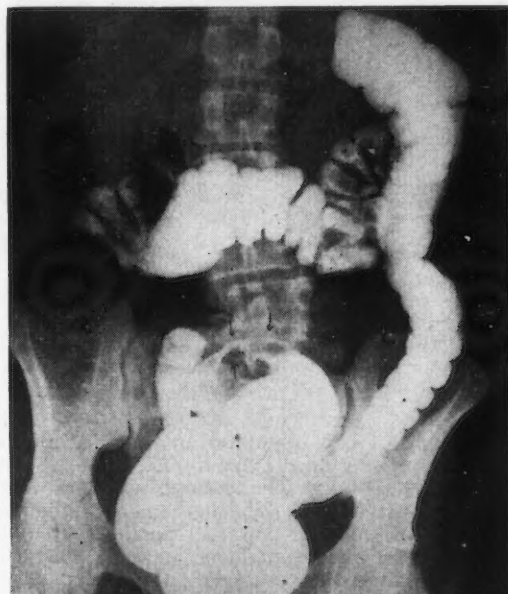


Fig. 1a

Fig. 1a.—Note the 4-inch irregularity in the rectosigmoid. Fig. 1b.—Spot film of the lesion noted in the barium enema film of July 15, 1946.



Fig. 1b

R.R., a 41-year-old woman, mother of two children aged 12 and 7 years, complained of low mid-back ache present for seven years. It had become more severe 10 days before her admission to hospital on July 8, 1946. For the previous year she had suffered from constipation, the stools being of small calibre. When she menstruated she noted that the faeces were streaked with bright blood. Frequency, and the sensation of being unable to empty her urinary bladder completely, were present. She was afebrile. The leukocyte count was normal, the sedimentation rate rapid.

The lower half of the abdomen was sensitive. The uterus was retroverted, the left adnexa palpably enlarged. There was diminished pain sensitivity on the dorsum of the right foot, and tenderness over the fourth and fifth lumbar vertebrae. Congenital malformations of the fourth lumbar and first sacral vertebrae were noted roentgenologically.

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A barium enema on July 15, 1946, revealed a 4-inch (10 cm.) irregularity with corresponding narrowing of the recto-sigmoid. The remainder of the large bowel filled well (Figs. 1a and 1b).

Proctoscopic examination revealed a polyp on the vaginal side of the rectum, 21 cm. from the anus. Close by, a second flat, slightly ulcerated polyp, 1/2 inch (1.25 cm.) in diameter, was also seen. The surrounding mucosa was injected and bled readily upon instrumentation. When the instrument touched the second polyp, it produced a pain reminiscent of her backache. Beyond the polyps, the lumen of the gut was narrowed by what was interpreted to be a mass causing external compression. Both polyps were biopsied. The roentgen ray and proctoscopic findings both suggested new growth.

The tissue removed for biopsy consisted of four small irregular friable fragments of grey and red tissue, 1 to 4 mm. in diameter. In two fragments rectal mucous membrane could be identified. Here, rectal glands were lined by single layers of regular columnar epithelial cells. These cells showed no alteration in nuclear polarity. The basement membranes were sharply defined. The balance of the surface in these two fragments showed ulceration and was infiltrated by polymor-

phonuclear leukocytes, lymphocytes and plasma cells lying in moderately vascular granulation tissue. The deeper portions of these and the other two fragments were composed of a cellular type of tissue in which numerous glandular spaces were encountered. These glands were somewhat irregular in shape but were lined by single layers of low columnar to high cuboidal epithelium, indistinguishable from epithelium which lines endometrial glands (Fig. 2). The cells composing these glands were regular in size, shape and staining quality, and basement membranes were sharply defined. Within and about some of these glands, moderate numbers of well-preserved red cells were encountered. About some of the glands, the stroma was more cellular than normal, spindle-shaped, and resembled the stroma seen in endometrium. The entire tissue was diffusely infiltrated by lymphocytes and scattered polymorphonuclear leukocytes.

Diagnosis.—Endometriosis of rectum, the site of subacute, non-specific ulcerative inflammation.

A laparotomy was performed on July 19, 1946. The uterus, which was not enlarged, was pulled over to the



Fig. 2.—Original proctoscopic biopsy specimen showing typical rectal mucosa at top, adjacent ulceration and underlying endometriosis. $\times 30$.

left. The left Fallopian tube and ovary were fixed in the pouch of Douglas, and surrounded by a mass of hæmorrhagic tissue. The posterior surface of the uterus was covered by dark red and purple implants, 1 to 30 mm. in diameter. The rectosigmoid was covered by an adherent, 2 cm., reddish-purple mass which dimpled the serosa and appeared to be growing through the wall of the bowel. Some of this tissue was removed for histological examination. A subtotal hysterectomy, bilateral salpingo-oophorectomy, and appendectomy were carried out. The diagnosis of widespread endometriosis was confirmed (Fig. 3).

Eleven weeks after the operation, the barium enema examination was repeated. The findings were similar to those noted before the operation. A proctoscopic biopsy obtained nine months after the operation revealed endometrial tissue still present in the rectum (Fig. 4). The patient was therefore given a course of deep x-ray

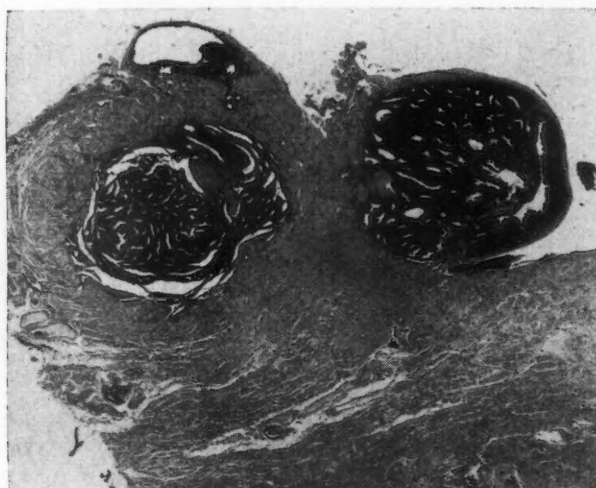


Fig. 3.—Endometrial implants on serosal surface of uterus, $\times 14$. This was part of the generalized endometriosis found at laparotomy.

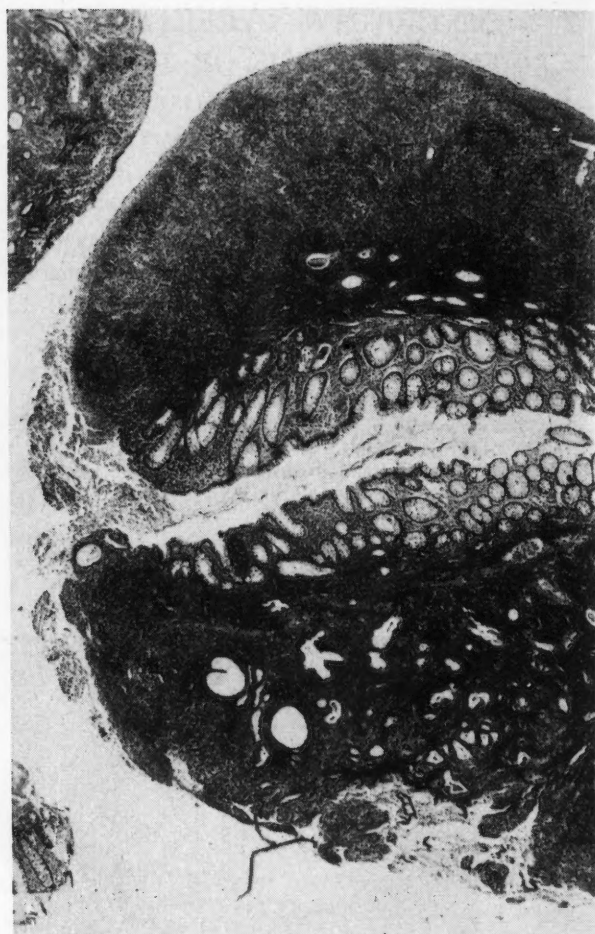


Fig. 4.—Rectal biopsy specimen taken 9 months after laparotomy. Note invasion of rectal wall by still viable endometrium. The rectal mucosa in this specimen is intact. $\times 40$.

therapy. Tissue obtained by proctoscopic examination eight months later (January 27, 1948) showed granulation tissue only. The patient was now having normal bowel movements, but the lumen of the bowel at the site of the lesion was still narrower than normal; the wall was, however, more pliable. On May 9, 1949, the proctoscopic examination revealed a slightly narrowed lumen at the original site, and minimal local colitis. A barium enema examination on May 10, 1949, almost three years after her operation, revealed a spastic sigmoid colon. This patient's bowel habits are now regular. When last examined on January 4, 1954, she was free of her original complaints.

DISCUSSION

Endometriosis should be considered in the differential diagnosis of abdominal pain, rectal pain, and lumbosacral backache, once menstruation has been established.¹⁻³

Constipation may be worse at the menstrual cycle or occur only during it. Less frequently, diarrhoea is noted under similar circumstances. Some patients complain of rectal pain when taking an enema, after which a little bloodstained mucus may be passed. Weight loss is seldom a feature of endometriosis.

The pelvic findings are important but hardly specific. The pelvis may be frozen. There are also instances when dense submucosal nodules may be palpated on the rectal side of the vagina. Meigs⁴ states that a characteristic finding is the beaded or shotty feeling in the cul-de-sac. A rectovaginal examination may reveal a thickened, tender lesion on the rectovaginal septum or rectum. When a mass can be palpated per rectum, the overlying mucosa is usually reported to be smooth and non-adherent. The findings may not be constant, for recession may occur after the menses. The signs and symptoms may be intensified if follicular hormone is given. Although the above findings, including the presence of a cyst of the ovary, may suggest the possibility of endometriosis, the presence of a mass in every instance demands the exclusion of the most important possibility, namely new growth.

In a series of 569 cases of endometriosis, Haydon³ found the sigmoid involved in 8 cases, and the rectum in 14. Sixteen of his patients were symptom-free. Green-Armytage⁵ discovered invasion of the rectovaginal septum in 12 of 38 patients. Mikulicz-Radecki⁶ reported 100 cases of recto-uterine endometriosis. Jenkinson and Brown⁷ reported involvement of the rectosigmoid in 47 of 117 cases. In about 50% of their cases, the implants did not attain a size sufficient to produce signs of rectosigmoid obstruction. The average duration of bowel symptoms in the series reported by Jenkinson and Brown⁷ was 3.3 years in the group of 21 patients with obstructing lesions of the rectosigmoid. It was 2.3 years in their group of 26 patients with rectosigmoid lesions of the non-obstructive type.

According to Cullen,⁸ hard, deep, indurated implants may develop in folds of peritoneum as palpable masses in the rectovaginal wall, between the posterior wall of the uterus and rectum, and in the cul-de-sac. The serosal and muscular coats of the rectum and colon, the mesentery and epiploid appendages may all be involved. There may be surface puckering of the serosa and muscularis which by itself, and by inspection and palpation, cannot be differentiated from carcinoma.

Smith⁹ reported associated malignancy in 7% of his cases of endometriosis. Thomson¹⁰ observed malignant degeneration of the muscle elements of a rectovaginal adenomyoma with metastases to the lungs. Somewhat similar cases

were reported by Lockyer.¹¹ Braine¹² reported a case of rectal carcinoma concomitant with a stenosing rectosigmoidal endometrioma. Jose and Hanson¹³ found a carcinoma of the sigmoid with endometrial tissue in the pelvic pouch and vaginal fornix simulating metastatic carcinoma in the regional lymph nodes. Nylander¹⁴ reported a spindle cell sarcoma of the rectum which contained endometrial tissue. Tuthill¹⁵ reported malignant endometriosis of the ovary in a girl aged 19.

According to Jenkinson and Brown,⁷ endometriosis of the rectosigmoid is characterized roentgenologically by a defect 4 to 7 inches long, with sharp irregular borders and intact mucosa. Inconstancy of the filling defect and fixation of the bowel, which is exquisitely tender to palpation, were other findings noted. In the cases reported by Patton and Patton¹⁶ the contrast enema demonstrated a filling defect high in the sigmoid. The mucosal pattern was preserved, and pressure by an extrinsic mass was suggested. A similar finding was reported by Josefsson.¹⁷

Proctoscopy was done on 18 of Mayo and Miller's¹⁸ 38 patients; in 15 there was some narrowing of the lumen of the gut. That the mucosa may bleed readily was noted by Bazy, Blondin and Chene.¹⁹ In several instances, puckering of the mucosa over the area of involvement was noted. In none was the presence of mucosal ulceration noted. In our patient's case the mucosa was ulcerated. Polyps which proved to be the seat of endometriosis were also noted. In addition, there was evidence of external compression of the rectum.

Cattell²⁰ in 1932 reported that he had operated upon a patient with obstruction of the rectosigmoid in whom the preoperative diagnosis was carcinoma. This patient was subjected to a two-stage abdominoperineal resection for an endometrioma which had extended through the muscular wall and was adherent to the mucosa which was not ulcerated. McKittrick²¹ reported the case of a 64-year-old patient who showed upon proctoscopic examination a firm polypoid mass. The unqualified x-ray diagnosis was of carcinoma. The intussuscepted tumour of the sigmoid was resected and an anastomosis performed for what proved to be endometriosis. Cattell²⁰ also reported three other cases. In two, he performed Mikulicz resections, in the third a bilateral oophorectomy. Hepburn²² reported a two-stage Mikulicz resection for a hard, nodu-

lar, infiltrating endometrial lesion situated opposite the mesenteric border of the sigmoid, the lumen of which was almost completely occluded. Eggers²³ reported three resections, and an instance in which bilateral oophorectomy was the treatment of choice. Patton and Patton¹⁶ performed a colostomy, followed later by a bilateral salpingo-oophorectomy, a resection of the diseased segment of the bowel and an end-to-end anastomosis. Surgically treated cases have also been reported by Bartlett,²⁴ Okinczyc,²⁵ Schofield and Bacon,²⁶ and Papin.²⁷

Surgery and x-ray therapy are safe and effective forms of conservative treatment. Both may be necessary in a given case. Neither the ulceration of the mucosa nor the irradiation effected permanent changes in our case.

SUMMARY

A case in which endometriosis of the rectum produced obstruction of the rectum and ulceration of rectal mucosa and in which the diagnosis was established by proctoscopic biopsy has been reported. This appears to be the first recorded instance of ulceration and definitive diagnosis established by rectal biopsy. A cure was effected by hysterectomy and salpingo-oophorectomy, followed by x-ray irradiation.

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HIDDEN ANVIL FRACTURE OF THE SEVENTH CERVICAL VERTEBRAL BODY

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SATISFACTORY RADIOGRAPHS of the entire cervical spine are difficult to obtain even under the most favourable circumstances. This applies particularly to the lower two cervical vertebrae, for these are obscured by the clavicles, the scapulo-humeral bony masses, and the bulky shoulder muscles. Hence heavy-set, short-necked, square-shouldered patients suspected of having lower cervical spine disease present a special challenge.

Some of the difficulties encountered in radiography of the lower cervical spine are emphasized by the following case report. A simple manoeuvre that ensures a clear lateral view is illustrated. A bony landmark, assisting the interpretation of the antero-posterior and oblique views, is noted.

While cutting a tree limb, a 28-year-old man slipped and fell 15 feet to the ground. He was admitted to the Toronto General Hospital within an hour. His chief complaint was of pain between the shoulder blades and pain in the mid-chest anteriorly. These pains were aggravated by trunk and neck movements, deep breathing and movement of the stretcher.

The patient was six feet tall, weighed 215 pounds, was short-necked and square-shouldered. Careful passive movements of the head and neck produced pain at the base of the neck radiating down between the shoulder blades. Pressure over the spinous processes and supraspinous ligaments in the cervicothoracic region elicited localized discomfort. Neurological examination did not reveal any evidence of nerve root compression or irritation as reflected by changes in reflex activity, motor power or sensory appreciation.

Radiographs: The first views of the cervical spine were unsatisfactory because the lateral showed nothing below C 5 (Fig. 1); the rest of the cervical spine was obscured by the massive shoulder girdle. The antero-posterior view revealed gross asymmetry of the neurocentral facets between C 6 and 7 (Fig. 2). On the left side the neurocentral facets were widely separated, while on the right they were practically superimposed. Attention was now focused on this level and numerous views, using various manoeuvres, were attempted.

The resulting oblique view of the left side (Fig. 3a) showed a subluxation of the inferior articular facet of C 6 and a fracture of its inferior margin. In addition the smooth outline of the intervertebral foramen was broken by a step deformity of the neurocentral facets (Fig. 3a). A slightly better lateral was obtained when manual counter-traction was applied to the wrists (Fig. 3b). This disclosed an intact C 6 and suggested a chip fracture of the anterosuperior portion of C 7.

It was felt that the x-ray findings, although minimal, warranted the diagnosis of a fracture

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Fig. 1.—First lateral views obtained on admission. Note shoulder girdle shadow obscuring lower vertebrae.

dislocation of the cervical spine. The patient was therefore admitted to hospital and skull traction was applied with a view to reducing the subluxation. After three days skull traction was increased five lb. at a time from 20 lb. to 45 lb. over a period of 25 minutes. The patient's neck was then extended a few degrees and the traction reduced to 15 lb. After this manoeuvre the patient stated that he was very much more comfortable and could rotate his head freely in both directions.

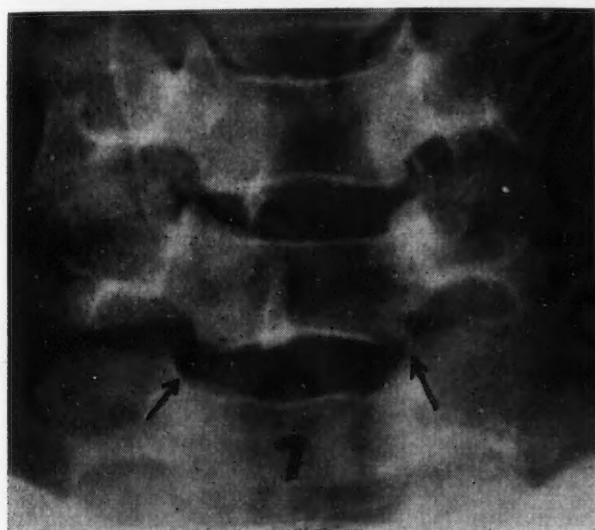


Fig. 2.—A.P. view of lower cervical spine. Tube tilted towards head 15 degrees. There is but little spinous process deviation, yet there is clear-cut asymmetry of the neurocentral facets between C 6 and C 7, as marked.

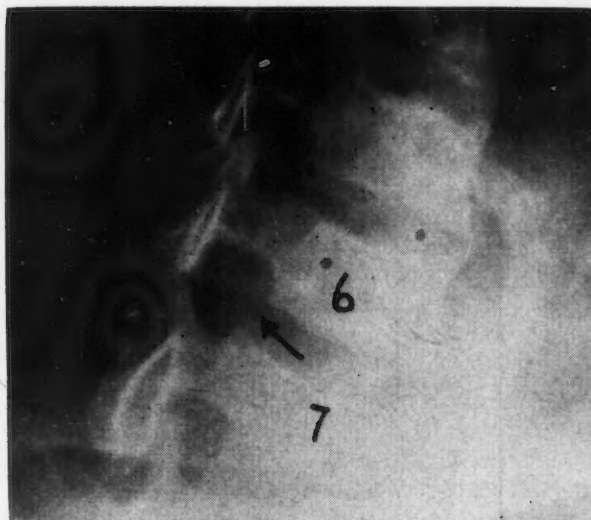


Fig. 3a.—Repeat oblique views show jumped posterior facet C 6 forward on C 7 with chip fracture inferior margin of inferior facet C 6. Note step deformity at neurocentral joint, as marked.

Radiography of his cervical spine was now repeated. In order to obtain a better lateral projection the following technique was employed. Manual traction was applied to the skull tongs, and counter-traction was applied by pulling on



Fig. 3b.—Repeat lateral film with manual traction. C 6 now revealed. Rotation evident as seen by lack of superimposition of posterior facets. Note at lower end (query) bony chip of body C 7, as marked.

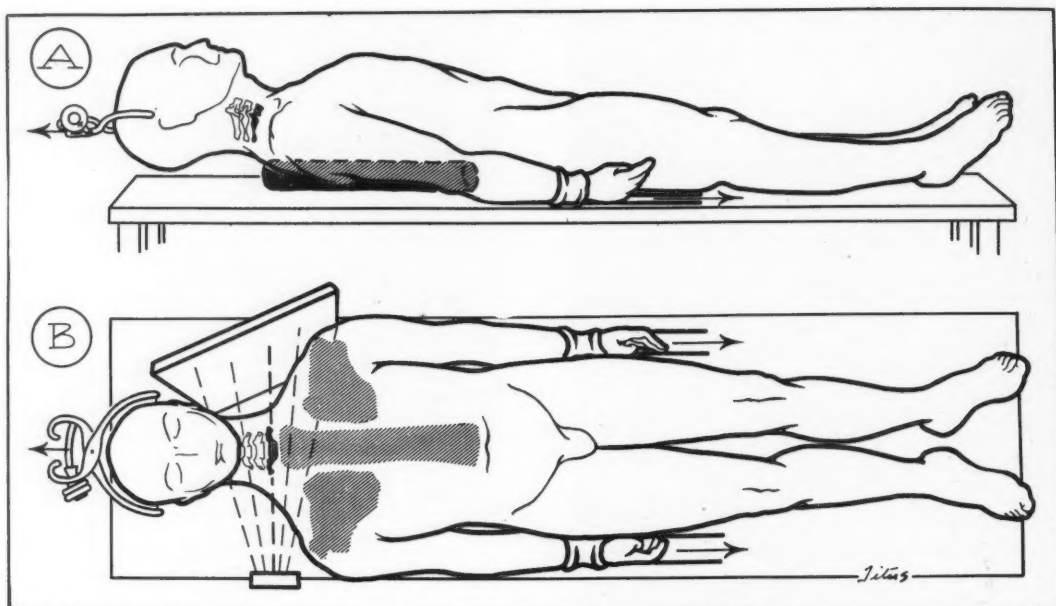


Fig. 4.—Diagram of positioning for lateral view of lower cervical spine. (C 7 blocked in.)

the patient's wrists. A bulky rolled-up towel was placed between the scapulæ, allowing the shoulder masses to drop backwards in addition to being pulled downwards by the wrist traction (Fig. 4). The resulting radiograph was unexpected and revealing (Fig. 5). The anterior half of the seventh cervical vertebra had been split off in a coronal plane. This fact had never been previously suspected. The shape of the fragment suggested that the mechanism of the fracture was forced flexion of the sixth cervical vertebra, allowing the antero-inferior border to strike the upper surface of the seventh cervical vertebra and split it. The lateral view also showed that the interspinous space between C 6 and 7 was increased. The x-ray appearance sug-

gested that the fracture must be associated with gross damage to the intervertebral disc, subluxation of the posterior facet, and rupture of the posterior interspinous ligament. The segment therefore was grossly unstable and it was felt that a localized cervical fusion between C 6 and 7 was indicated.

DISCUSSION

The neurocentral facets afford another landmark for determining the anatomy of cervical spine injuries. An asymmetry of these facets may be the only radiographic evidence of severe damage to the spine. It is imperative to obtain a good lateral view, and in the lower cervical spine this can be extremely difficult to record. The manoeuvre described above was found to be sufficiently satisfactory for subsequent radiographs to be taken with a portable x-ray unit, thus avoiding the difficulties of transportation.

The technique may be variously modified as desired. If ice tongs have not been applied, a padded Sayer's sling or manual occipito-mental traction with a towel slit longitudinally in its middle so that it can be slipped under the chin and occiput is a satisfactory substitute. Instead of a rolled towel, a loaf-shaped piece of balsa wood or a tightly packed sandbag may be placed between the scapulæ. Wide flannel bandages tied about the wrists and fixed to the foot of the bed providing fixed counter-traction may satisfactorily replace awkward manual counteraction.

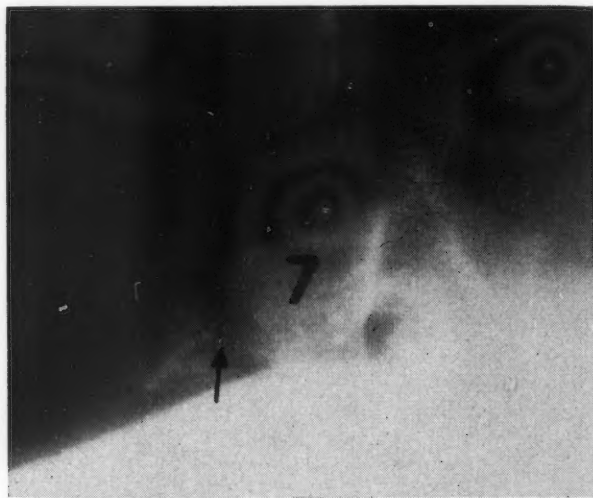


Fig. 5.—Lateral view of lower cervical spine obtained following use of technique pictured in Fig. 4. Note triangular-shaped anterior fragment split off in coronal plane from C 7.

REVIEW ARTICLE

OSTEOPOROSIS*

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THE MEDICAL COMPLEXITIES posed by diseases of the soft tissue coverings and contents of the human skeleton tend to limit the attention paid to bone itself. This does not apply to the localized diseases of bone which tend to make their presence known, but to those generalized bone diseases which, acting through some subtle metabolic change, progress unobtrusively. One such insidious change is the atrophy of bone which characterizes osteoporosis, a change which may be so benign and slow-moving that its presence may not be recognized, its frequent incidence not appreciated, its incapacitating sequelae not respected and its treatment not initiated until after the appearance of irreversible postural abnormalities. Investigation in recent years has added greatly to our understanding of osteoporosis and has provided means of diagnosis, specific treatment and methods of prevention. It is with some of these newer concepts that this paper is concerned.

PHYSIOLOGICAL CONSIDERATIONS

Bone is supportive in function only because of its mineral impregnation. Of much greater importance is the fact that the essence of bone is connective tissue and that this organic matrix of collagen and intercellular substance (osteoid) comprises half the total skeletal weight. It is the special function of this soft tissue trellis to store minerals such as calcium, phosphate and carbonate, thereby creating a rigid framework for body support. About 99% of total body calcium is stored in bone in combination with phosphates, carbonates, hydroxyl and other ions in the form of innumerable small crystal plates having wide surface area and shallow depth, placed along the long axis of the collagen fibres. This crystal form has been variably estimated to provide from 100 to 200 acres of surface area in a 70-kg. man, and is admirably adapted to respond to rapid demands for storage or release of mineral in the maintenance of equilibrium of the body fluids.

From the metabolic viewpoint, bone is highly active and, as in other tissues of the body, resorption and replacement proceed unceasingly. Normally, the rates of formation and resorption of bone are in dynamic balance. Osteoblasts are the osteoid-producing cells and their activity depends upon many factors, including adequate stimulation by hormones and skeletal stresses and strains. They also elaborate the enzyme alkaline phosphatase, the function of which is

not yet well defined. The action of increasing local phosphate ion concentration, previously ascribed to this enzyme, is no longer generally accepted. It is now suggested that it may be essential in the formation of protein matrix and in conferring on the matrix the property of calcifiability.¹ The mechanism of bone resorption is not understood. It is believed that osteoclasts, cells similar to osteoblasts and possibly of the same origin, are concerned with this activity. The ions released during bone resorption are conserved by the body and re-utilized in calcifying newly formed osteoid.²

CHANGES IN BONE WITH AGE

Total skeletal mass changes with age. Its greatest weight is reached between the ages of 25 and 30 and there follows an irregular decline in weight as the bone becomes more porous in later life.³ This physiological change which bone shows in common with other tissues is variable in different individuals and when marked presents the clinical picture of osteoporosis. It is believed to be due to a gradual reduction in bone matrix formation while bone resorption continues at the normal rate. As a result, more bone salt is removed than can be re-deposited and the unutilized mineral is excreted from the body by the kidney. Quantitatively, the amount of bone salt lost in this way is not sufficiently great to produce any notable rise in renal calcium excretion or in blood levels, but over the years the depressed rate of osteoid formation and the continued loss of calcium inevitably result in osteoporosis. Eventually an equilibrium is reached between bone formation and resorption.

DIFFERENTIATION OF OSTEOPOROSIS

Osteoporosis is a specific diagnosis, to be used only in those conditions in which bone deficiency exists because of inadequate matrix formation. Although reduced in amount, the matrix is normally calcified. Porousness is due to enlargement of the canals or formation of abnormal spaces within the bone. Normal blood levels of calcium, inorganic phosphate and alkaline phosphatase are to be expected.⁴

The term *osteomalacia* is reserved for those conditions in which bone deficiency exists because of inadequate calcification of matrix although organic matrix production is normal. This form of rickets in the adult may lead to deformities because of the abnormal softening of bone. It is usually secondary to deficient intakes of calcium or vitamin D or both. Serum levels of calcium and inorganic phosphate may be normal or low, and the calcium x phosphate product expressed in milligrams per cent is less than the normal adult range of 30-40.² Bone weakening with osteoblastic stimulation may lead to elevation of serum alkaline phosphatase levels.

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Prolonged *hyperparathyroidism* results in bone deficiency and may be thought of as a state in which the rate of bone destruction exceeds that of new bone formation. Typically, there is elevation in serum level of calcium, depression of inorganic phosphate level and, in the presence of bone lesions, elevation of serum alkaline phosphatase.

As Albright has emphasized, this differentiation is important from the radiological viewpoint, since the bone demineralization common to all three conditions may be erroneously referred to as "osteoporosis".

ETIOLOGY AND CLASSIFICATION OF OSTEOPOROSIS

Fragilitas ossium, a rare disease which in some respects resembles osteoporosis, may be apparent from birth, and is believed to result from an inherent inability of the osteoblasts to produce normal osteoid. With this exception, osteoporosis is commonly associated with a group of clinical conditions, one or more of which may be of etiological importance in any individual.

I. SENILE OSTEOPOROSIS

There is a tendency for senile osteoporosis to appear in families, passing from parent to offspring, suggesting that such individuals are prone to develop more severe senile bone changes. The importance of age alone is unknown, but it seems likely that senile atrophy of bone is the result of a number of superimposed factors common to old age, including the endocrine disturbances of senile gonadal hypofunction and the postmenopausal state, the general decrease in body activity with reduction in skeletal stresses and strains and, possibly, nutritional deficiencies.

II. ENDOCRINE FACTORS

The growth and health of bone is probably influenced by several endocrine glands but it is the antagonistic effect between the *adrenal* and *gonadal hormones* which appears to be of primary importance. Whereas the glucocorticoids of the adrenal cortex tend to decrease skeletal mass by an anti-anabolic effect on nitrogen metabolism, retention of bone mineral and nitrogen is enhanced by oestrogens, testosterone and the adrenocortical androgenic hormone. It is probably by virtue of alterations in this hormonal balance that the aging pattern of bone and osteoporosis appear. Thus, decreasing testosterone levels in older men may result in senile osteoporosis; climacteric loss of oestrogens may lead to "postmenopausal" osteoporosis and probably is responsible for the high female incidence of osteoporosis, and in Cushing's syndrome, osteoporosis is probably due to the abnormal elevation of glucocorticoids. The defec-

tive bone growth and osteoporosis associated with artificial menopause in younger women and also occurring in primary gonadal insufficiency in either sex is believed to have a similar explanation.

The relationship between osteomalacia and pregnancy is well known, especially in the Orient. It has been noted in England that there also appears to be some relationship between osteoporosis and pregnancy. In elderly women, the incidence of osteoporosis in those who are multiparous is almost double that of those who are nulliparous.⁵ Recently, severe spinal osteoporosis has been reported in younger women, appearing shortly after pregnancy. In the latter instance, it has been suggested that the osteoporosis is related to the increase of adrenocortical activity occurring during pregnancy.⁶ There is controversy as to whether the anti-anabolic effect of the steroids is still exerted in the face of the concomitant rise in oestrogen levels during pregnancy.

Although osteitis fibrosa generalisata is the usual bone lesion in *hyperparathyroidism*, it is interesting that demineralization of the spine may appear early in the disease before the development of the more typical bone lesion.

In *thyrotoxicosis* the increased metabolic rate and nitrogen utilization have been suggested as a cause of deficient matrix production leading to hypercalciuria and osteoporosis.

The gonadal insufficiency occurring late in *acromegaly* is a postulated cause of the osteoporosis occasionally present.

In the interval during which *ACTH* and *cortisone* have become available for therapeutic use, an increasing number of reports have appeared commenting on the severe osteoporosis complicating prolonged therapy. This bone change has occurred more frequently in immobilizing diseases such as rheumatoid arthritis, in elderly people and in women, and has been ascribed to the anti-anabolic effects of the hormones.⁷ The higher incidence in females has been attributed to the fact that oestrogens are less effective than testosterone in antagonizing the metabolic effects induced by cortisone.⁸ This explanation may require modification in the light of the recent observation that cortisone does not appear to inhibit osteoid formation in animal rickets or scurvy.⁹

III. OSTEOPOROSIS OF DISUSE

The importance of the sum of those forces acting upon bone during normal weight-bearing and muscular contraction is indicated by the local or generalized osteoporosis resulting from the absence of such mechanical factors during immobilization.¹⁰ This lack of bone stress is believed to account for the local osteoporosis occurring in immobilized fractured bone, and for generalized osteoporosis appearing in paralytic poliomyelitis or during prolonged bed rest.

Strains such as tension, torsion, pressure or shearing forces exerted on bone during weight-bearing, are countered by stresses, or forces within the bone, which resist deformity. These, as well as the complicated stresses produced by muscular action on bone, determine the thickness, closeness of spacing and arrangement of the trabeculae.⁵ Such forces may produce only molecular movement in bone, but whatever their mechanism they appear to be of fundamental importance in bone health and in osteoblastic stimulation.

IV. NUTRITIONAL DISTURBANCES

Inadequate *dietary intake* of mineral and protein appears to be an unimportant cause of osteoporosis in Canada. Severe and prolonged protein deficiency may lead to osteoporosis in the occasional case of steatorrhoea. Much more commonly, however, this illness results in osteomalacia secondary to inadequate absorption of vitamin D and calcium.

Vitamin C deficiency may cause osteoporosis in children, and it is of interest that blood levels of vitamin C in elderly people have been found to fall in the low normal range of young individuals.¹¹

V. OTHER FACTORS

The problem of the etiology of "idiopathic" osteoporosis occurring in younger men and in premenopausal women is unsolved. In women, this syndrome may perhaps be related to the syndrome of "postpregnancy osteoporosis" with delayed appearance of bone changes. Although it may occur in male siblings, the reason for its appearance in young men remains obscure.¹²

CLINICAL AND RADIOLOGICAL FEATURES OF SENILE OSTEOPOROSIS

Although over 800 cases of generalized osteoporosis have been reported in the literature in the past 27 years, this figure undoubtedly fails to indicate its real frequency.⁵ Radiological survey of asymptomatic elderly people has revealed the presence of spinal osteoporosis with asymptomatic vertebral compression fractures in one out of every four people between the ages of 60 and 95 years.¹³ In the group of reported persons, osteoporosis has occurred six times more commonly in women than in men and it shows an age range from 50 to 80 with a peak incidence in the 70-80 year group.⁵

Back pain, so often described as the common and characteristic symptom of osteoporosis, is frequently absent. The most common manifestations are spinal deformity and imperceptible loss in height associated with no acute painful episode. Frequently, fracture in an extremity from trivial injury provides the clue to the presence of osteoporosis. Back pain, when present, may occur spontaneously or during mild vertebral strain, is usually acute in onset and is frequently

incapacitating. There is often radiation around the trunk or down the legs and aggravation of pain by attempted movements.

With back pain, spinal mobility is severely restricted and postural muscle spasm may be marked. The fractured vertebrae can often be distinguished by local pain and tenderness over the involved vertebral spines. In addition, there is often a rounded thoracic kyphosis which may extend into the lumbar spine and replace the normal lordosis. As the kyphosis becomes more severe, a cervico-thoracic lordosis may develop—a compensatory hyperextension of the cervical spine to facilitate vision—and may result in a more obvious hump in the region of the vertebra prominens. Loss of height due to vertebral compression fractures is often indicated by a narrowing of the distance between the lower costal margin and the iliac crests; in the presence of multiple compression fractures, the costal margin may actually lie within the false pelvis. A loss of two or three inches in height is not uncommon. The redundancy in length of abdominal skin resulting from this loss of trunk height often gives rise to a transverse skin fold in the upper abdomen.¹⁴

The essential radiological feature of vertebral demineralization is quite non-specific and, as previously mentioned, is compatible with the presence of osteoporosis, osteomalacia, hyperparathyroidism, multiple myeloma and metastatic disease. In osteoporosis the spine is the site of predilection, followed in order by the pelvis, ribs and hips. The skull is usually uninvolved. A sequence of radiological bone changes has been described during the development of osteoporosis; but in the late stages, at the time the patient is usually examined, the decrease in bone density is such that there is poor contrast between bone and soft tissue, the cortex becomes a fine line and the remaining trabeculae are widely spaced and tend to run in a vertical direction.¹⁵ Anterior wedging and compression of vertebral bodies is often present. With multiple vertebral compressions, the spinous processes may be crowded together and there may be false joint formation between them. The disc spaces are frequently narrowed but the thinning of the vertebral end-plates may allow expansion of the discs resulting in biconcavity of the vertebral bodies—the so-called "codfish vertebra". It has been variously estimated that a loss of from 30 to 60% of bone calcium must occur before radiological bone change becomes recognizable.¹⁶ Thus, radiological decalcification signifies that gross inroads have been made on the remaining calcium content of the bone involved. There is very little radiological evidence to show that the trabecular change in osteoporosis is influenced by treatment even when the latter is prolonged. Increased density and thickness of the cortex has been noted but there appears to be no replacement of lost medullary trabeculae. From personal

experience and from published reports, it is evident that attempts to quantitate bone density changes during the progression or treatment of osteoporosis by densitometric measurements have had dubious success, and to my knowledge no practical method is yet available.

Serum calcium, inorganic phosphate and alkaline phosphatase levels are normal in osteoporosis, and although the serum albumin tends to be low, total proteins are usually within the normal range. There is some recent evidence to indicate that bone avidity for infused calcium is less in osteoporosis than in normal states of calcium metabolism. This work requires further confirmation but may prove to be of diagnostic value.¹⁷

DIAGNOSIS OF SENILE OSTEOPOROSIS

Differentiation between postmenopausal and senile osteoporosis is of little value since both seem to represent the same disease. Senile osteoporosis when well marked is highly characteristic and not likely to be confused with any other disease. The specific history, biochemical abnormalities and radiological findings serve to clarify the diagnoses of osteomalacia and hyperparathyroid bone disease, both of which, of course, are very uncommon. The characteristic body habitus and laboratory findings in Cushing's disease and acromegaly usually aid in the elimination of these possibilities. Similarly, little difficulty should be encountered in the diagnosis of thyrotoxicosis, except in the occasional instance of "masked" thyrotoxicosis in elderly people. Idiopathic osteoporosis is a diagnosis of exclusion, differentiated from senile osteoporosis only by its younger age incidence.

The association of anaemia with skeletal demineralization should arouse suspicion of the presence of multiple myeloma or of secondary neoplasm, especially when the patient has lost weight and is obviously ill. Anaemia is an almost constant early finding in *multiple myeloma* and although typical multiple bone lesions are commonly present, in 14% of cases the sole skeletal abnormality may be a diffuse demineralization. The skull is frequently involved by this demineralization, in contrast to senile osteoporosis. The diagnosis is suggested by an increase in plasma cells in the bone marrow and occasionally in peripheral blood, and is supported by the presence of Bence-Jones proteinuria and elevation of serum globulin levels.¹⁸ Similarly the presence of *primary malignant* disease elsewhere in the body must be excluded by physical, endoscopic, radiological and histological examination, in order to rule out skeletal metastatic disease producing diffuse demineralization.¹⁹

PREVENTION OF OSTEOPOROSIS

Since the underlying etiology of osteoporosis is unknown, specific measures of prevention are not available. Indeed, in the familial form of

the disease, the development of osteoporosis may be the inevitable result of an inherent constitutional defect. However, the onset of osteoporosis can be delayed and its serious manifestations averted by the avoidance of those factors known to accelerate the disease process. In elderly people, osteoporosis can be best prevented by continued activity and avoidance of the immobilization of prolonged bed rest. When bed rest is essential, the patient should be instructed to perform simple exercises of the extremities and back and should be stimulated to move about in bed. Early ambulation is important even if it consists only of sitting in a chair. Awareness of the accelerating effect of ACTH and cortisone should dampen the enthusiasm with which these drugs are sometimes administered and reduce the duration of treatment to a minimum.

TREATMENT OF OSTEOPOROSIS

I. EXPLAINING THE CONDITION AND ITS TREATMENT TO THE PATIENT

One should explain that thinning and weakening of the bones occurs commonly in older people and that the cause is not well understood. In the prevention of deformities and bone pain, it is essential for the patient to co-operate actively in maintaining continued activity and good posture, and to avoid bone trauma. There is as yet no convincing evidence that prolonged hormonal therapy will improve bone strength; although bone pain may be relieved at the onset of treatment, future attacks of pain may not be prevented.

II. PREVENTION OF DEFORMITIES

Firm straight-backed chairs and bed fracture boards aid in the prevention and treatment of spinal deformities, and the patient should be instructed accordingly. Slouching in easy chairs or on pillows should be deprecated.

During controlled movements, when supported by the musculature, bone can withstand great stresses but when this support is lacking, as during sudden unexpected stress, relatively minor force will produce fractures.⁵ Thus, patients should be warned to avoid sudden exertion involving the back such as lifting, pulling and pushing, and should be cautioned against the jarring movement produced when motoring over rough roads.

Muscular contraction may prove to be more important than weight-bearing in the stimulation of osteoblastic activity. Oscillating and vibratory beds will reduce calcium losses occurring in normal immobilized individuals,²⁰ and it has been suggested that this effect is due to repeated muscle pull on bone. The place of such mechanical devices has not yet been defined in the treatment of osteoporosis. On the other hand, the physician can and should devise a program of simple therapeutic exercises adapted for the

particular patient's need. Thus, in the presence of vertebral fractures, strenuous forward flexion of the spine is probably contraindicated, as is undue strain on the bone of an extremity which has undergone recent orthopaedic repair.

The therapeutic value of spinal braces is difficult to assess because most patients are reluctant to wear them.

III. HORMONE THERAPY

In elderly people, the positive calcium balance achieved during sex hormone administration has been attributed to the osteoblastic stimulation by oestrogens and the nitrogen-retaining effect of androgens. Greater calcium retention has been observed when the two hormones are given together than when either is given alone. Often, during such therapy, there is improvement in general muscle tone and bulk. This improvement in muscular contractility may also be important in osteoblastic stimulation.

In the dosage used, there is little danger of hormone-induced carcinogenesis; however, periodic prostatic examinations in men and regular interruption of oestrogen therapy in women are advisable precautionary measures. Although not a serious problem, hormonal side-effects vary in degree, in time of appearance, and in acceptability to the patient in different individuals, and must be dealt with accordingly. Infertility may occur in the male during androgen therapy and temporary water retention during oestrogen therapy; however, side-effects are chiefly of a cosmetic nature. Gynecomastia and decreased libido may appear during oestrogen therapy in men, whereas women treated with androgens may develop increased libido, deepening of the voice, facial hirsuties and frontal balding. In both sexes combined therapy tends to delay the appearance of these side-effects. Voice changes and hirsutism may appear with unusual rapidity in some women and may later prove to be irreversible. In susceptible individuals it is essential to interrupt testosterone therapy early before permanent changes occur.

Diethylstilboestrol (1 to 5 mg. daily), ethinyl oestradiol (0.02 to 0.06 mg. daily) and conjugated oestrogens or "Premarin" (1.25 to 2.5 mg. daily) are the commonly used oral oestrogenic agents. Nausea may be encountered during oral oestrogen therapy but it is usually relieved by changing to another oral preparation. Rarely, nausea persists in spite of such changes and it may be necessary to use oestradiol dipropionate in a dose of 5 mg. intramuscularly once weekly. In women, it is usual to administer oestrogen for four weeks and then to discontinue it for one week, to allow menstruation to occur. This interrupted therapy of "four weeks on, one week off" is continued indefinitely. It is unnecessary to interrupt oestrogen therapy in men in whom the same dosage is used combined with androgens.

Methyltestosterone "linguets" (10 to 30 mg. daily placed under the tongue) are commonly used for oral androgen therapy. In women, methyltestosterone is added to oestrogen therapy. The oral agent may also be used in men, but a greater effect may be achieved by using intramuscular testosterone propionate in a dosage of 25 mg. daily or 50 mg. every two or three days. Testosterone cyclopentylpropionate, a recently available long-acting form of testosterone, may be used to reduce the frequency of injections in a dose of 100 to 200 mg. intramuscularly every two to four weeks.

IV. DIET

The diet seldom requires modification but it is desirable to ensure an adequate daily source of protein. An average calcium intake (about 800 mg. per day) seems to be sufficient.²¹

Strontium is deposited in bone like calcium and is said to be absorbed independently of calcium even after maximal calcium retention has been attained. In the treatment of osteoporosis, however, the place of strontium is still controversial.²²

RESULTS OF TREATMENT

Response to hormonal therapy varies in different individuals and with the degree of osteoporosis. Obviously skeletal deformities causing postural abnormalities are not altered. Back pain may be relieved within a few days, although several months of treatment are occasionally required before pain subsides. In spite of continued treatment, back pain may recur, especially if the importance of activity and correct posture is ignored. Increase in general well-being is a frequent response, especially in women.

There is very little evidence to show that radiological remineralization of bone occurs during treatment. It is well known that positive calcium balance may be achieved by hormonal therapy, but such relatively small quantities of calcium are retained daily that a period of about five years must elapse before radiological bone change may be expected. Because of the impracticability of such prolonged balance studies, it is not yet established that hormonal therapy will result in continued calcium retention over prolonged periods. This is partly responsible for the lack of evidence of radiological improvement in bone during treatment.

SUMMARY

Senile osteoporosis is a common and important condition. It is an almost constant feature, in varying degree, of the later years of life and is believed to result from inadequate bone matrix formation. It usually develops slowly but its progress may be greatly accelerated by certain deleterious factors, with the result that

the bones become thin and fractures are common. Avoidance of these factors is believed to be important in the prevention of the serious complications of osteoporosis. Treatment commonly relieves bone pain but fails to correct bone deformity. As yet there is no precise way of measuring any beneficial effect that prolonged treatment may have on bone structure.

It is a pleasure to acknowledge the generous suggestions and advice of Professor R. F. Farquharson, Dr. K. J. R. Wightman and Dr. E. R. Yendt in the preparation of this manuscript.

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Clinical and Laboratory Notes

THE SYSTOLIC MURMUR IN THE FUNNEL-CHEST SYNDROME

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IN TWO PREVIOUS PAPERS^{1, 2} the author delineated certain electrocardiographic features seen in the funnel-chest syndrome. He also mentioned that in practically all cases in which the thoracic deformity definitely interfered with the effective diastolic space, a rough early systolic murmur was observed. This murmur was most apparent between the mitral and tricuspid areas along the side of the "funnel" formed by the chest wall.

Further, after operative lifting of the sternum, the murmur either disappeared or was greatly diminished in intensity, and it was suggested that this murmur might be caused by deformity of the mitral ring early in systole.

As this hypothesis could not be tested on a living heart, a heart was procured at autopsy, and to it was left attached about four inches (10 cm.) of aorta. The left auricle was dissected away, revealing a natural mitral valve. The index finger was inserted into the aorta to destroy the aortic valve cusps. When the autopsy-room hose bearing water running fairly slowly was inserted into the aorta and the latter grasped firmly, the mitral valve cusps came into apposition in the "closed" position with a snap. Then, with the other hand, the heart was compressed in the anterior-posterior position similar to the manner in which it would be deformed by the sternum and vertebral column in the funnel-chest syndrome. As soon as this was achieved, the edges of the mitral cusps wrinkled and the water shot through the gap. The irregular "wrinkling" along the edges of the cusps is probably responsible for the rough quality of the murmur, since it must produce a pattern of fluid turbulence vastly different from the smooth "soft" type of mitral murmur heard in pure rheumatic mitral regurgitation or that of myocardial dilatation.

This result seems to support in some measure the thesis that, in the funnel-chest syndrome, the mitral ring is deformed in full diastole; and that, as systole begins, the mitral valve, however normal it may be anatomically, is functionally incompetent. Of course, as systole proceeds, the ring will be able to assume a circular configuration and the valve will then become competent. This theory, however, does not explain the observed fact that the murmur did not disappear postoperatively in some cases, but was still present although greatly reduced in intensity. We could see at operation that adequate space was being provided for the heart, and therefore the mitral ring hypothesis could no longer obtain. It appears then that we must consider an additional postulate to explain this fact.

This syndrome is present from the first few months of life and is well established at an age of about 18 months. The infant goes on to grow as well as develop, the heart being unable to expand fully in the antero-posterior direction. This syndrome usually leads to a diminished exercise tolerance and so attracts attention in the third and fourth decades of life. Is it possible that the chordae tendinae, and probably the papillary muscles, which anchor the edges of the cusps, might not develop to their normal length, being either shorter or longer? Considering the altered shape of the mitral ring, could not the anterior chordae tendinae of the anteromedial cusp and the posterior chordae of the posterolateral cusp be shorter than normal? And, by the same token, could not the posterior chordae of the antero-

medial cusp and the anterior of the postero-lateral cusp be longer than normal? Then, when the ring becomes circular postoperatively, the valve would still be slightly incompetent. This involved explanation seems to the author to be the only way to account for the facts observed under these unique circumstances. Since none of our cases have come to autopsy, the author is unable to check the second postulate.

SUMMARY

A simple experiment was performed to account for the murmur heard in early systole in the funnel-chest syndrome. The results seem to justify the impression that this murmur may be caused by deformity of the mitral ring in early systole.

Another theory is advanced to account for the fact that the murmur does not completely disappear postoperatively in some cases.

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TREATMENT OF PSORIASIS AND OTHER CHRONIC DERMATOSES WITH EXTRACTS OF *RAUWOLFIA SERPENTINA*

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IN AUGUST 1954, it was learned that Genest and his co-workers¹⁻³ in Montreal had found that extracts of *Rauwolfia serpentina* were of value in the treatment of psoriasis. After correspondence with Dr. Genest, it was decided to treat a selected group of patients suffering from psoriasis in the Dermatology Clinic, Toronto General Hospital. The study was enlarged to include a few cases of atopic dermatitis and two of lichen planus. The drug† was in the form of Rauwiloid (alseroxylon) 2 mg. tablets, and Serpiloid (reserpine) 0.25 mg. tablets. Some patients were treated with one and others with the other, and no appreciable difference was noted in effect on their disease or in side-effects. The usual dosage was one tablet four times daily. If drowsiness was pronounced, the dosage was changed to two tablets at bedtime.

*From the Department of Medicine, University of Toronto, and Dermatology Clinic, Toronto General Hospital. Group Captain Caldbick is on leave from the R.C.A.F.
†Supplied by the Riker Pharmaceutical Co.

Side-effects were not a pronounced feature and consisted of slight drowsiness which usually disappeared within a week or two and nasal congestion which was persistent and annoying to some patients. There was definite diminution in itching and a tranquillizing effect, noted by both Rein and Goodman⁴ and Ferrara and Pinkus.⁵

CONDITIONS OF THE STUDY

1. Patients were chosen whose disease was either stationary or becoming worse.

2. Topical remedies remained unchanged during therapy.

3. Blood pressure readings were taken at each visit and notes were made of the patient's general condition and appearance of the eruption before treatment was started and at each visit.

4. Patients were chosen who agreed to persist with treatment for at least two months.

From September 1954 to March 1955, a group of 14 patients was treated. These patients reported regularly for observation and were given a supply of tablets sufficient for two weeks only at each visit. The following were treated: psoriasis, 9 cases; atopic dermatitis (eczema), 3 cases; lichen planus, 2 cases.

The group consisted of 7 males and 7 females and their ages varied from 18 to 52 years. The duration of their diseases varied from two weeks (lichen planus) to 24 years (psoriasis). Initial blood pressure readings taken on this group were all within normal limits and there was no appreciable fall in any of the patients during treatment. Some patients showed definite bradycardia after using the drug for months. Unfortunately this was not appreciated early in the test and was not carefully followed up throughout.

RESULTS

As might be expected in any new treatment, there were rather dramatic early improvements in at least four patients. In one patient, lichen planus cleared like magic but the other patient on the same drug showed only slight improvement. Two patients with psoriasis and one with eczema who at first responded dramatically relapsed while still on the drug, although the eczema did not become as severe as before treatment.

After following up these patients for periods varying from two to four months during treatment and in some cases for four months after cessation of treatment, one must conclude that there has been no real and lasting improvement in any with the exception of the one patient with lichen planus.

DISCUSSION

This is a small series and no sweeping conclusions should be drawn. We felt however that most of the improvement might be attributed

to a mild tranquillizing effect of the drug together with enthusiasm on the part of physician and patient for a new treatment, rather than to any specific effect.

Rein and Goodman⁴ noted a pronounced lessening of pruritus in most of their 60 cases, and also the tranquillizing effect previously mentioned. Placebo therapy resulted in a recurrence of previous symptoms. It is of interest that five of their patients with severe hyperhidrosis improved on reserpine. Side-effects noted by them included increased appetite, dreams and nocturia in addition to nasal congestion. Ferrara and Pinkus⁵ noted the improvements mentioned above and in addition saw improvement in five patients with neurotic excoriations.

SUMMARY

In view of the experience of three groups of workers (Genest *et al.*, Rein and Goodman, and Ferrara and Pinkus) who were all favourably impressed with the effects of extracts of rauwolfia in various dermatoses, it appears that this group of drugs has some value.

It is doubtful whether the drug will be of any lasting value in psoriasis, but it may have a place in those dermatoses which have a neurogenic or psychogenic background.

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COMMITTEE ON THE CLINICAL USES OF RADIOACTIVE ISOTOPES

CHAIRMAN'S REPORT TO THE FACULTY OF
MEDICINE, UNIVERSITY OF TORONTO,
DECEMBER 2, 1955

JAMES A. DAUPHINEE,* *Toronto*

IN THE SPRING of 1948 a Faculty Committee on the Clinical Uses of Radioactive Isotopes was set up by Dean MacFarlane of the University of Toronto Faculty of Medicine. This committee was established primarily to assist the Faculty in the clinical applications of these important new diagnostic and therapeutic tools, soon to be made available for medical use from the Canadian heavy water pile at Chalk River.

*Department of Pathological Chemistry, University of Toronto.

The committee members included representatives both from the clinical and from the basic science departments of the University. The terms of reference directed the committee to consider the types of clinical cases in which isotopes might be used with benefit both for investigation and treatment, to give thought to the safety measures which ought to be set up in relation to the handling of these potentially dangerous substances, to consider the ways and means for the establishment of a central "hot" laboratory from which these substances could be dispensed, and to make recommendations about the special instruments necessary for the measurement of isotopes and for detecting their presence.

With generous financial help first from the Department of Public Health, then from the Ontario Cancer Treatment and Research Foundation, and finally from the Atkinson Foundation, all these directives have been fairly satisfactorily accomplished. A "hot" laboratory, equipped to handle up to 300 mc. radioactive isotopes, and a counting room were set up first in the basement of the Banting Institute. More recently additional space has been obtained on the top floor of the same building and remodelled for work with radioisotopes. This isotope laboratory is under the charge of Dr. William Paul, a physicist, who is also responsible for the establishment and maintenance of the health radiation safety regulations; he is assisted in much of his work by Miss Amy Britton, a biochemist. For administrative purposes the laboratory is attached to the Department of Pathological Chemistry.

With the help of this laboratory and its staff the clinicians have been able to investigate and apply a large number of the possible uses of radioisotopes in clinical medicine. All proposed uses of radioactive isotopes in humans are reviewed by a small sub-committee on isotopes and must have its approval before they can be applied. Adequate opportunities for training in the uses of isotopes are available for physicians who wish to work in this field.

The following few paragraphs summarize briefly the work with radioisotopes which has been done and is being done in our school.

RADIOACTIVE IODINE, I¹³¹

One of the most useful and frequently employed isotopes is radioiodine. Dr. MacAllister Johnston and his group at the Toronto General Hospital have been and are employing this isotope in the investigation of thyroid and other endocrine disorders and are also using it in the treatment of suitable patients with hyperthyroidism and with cancer of the thyroid. Some indication of the amount of work being done by this group will be gathered when it is pointed out that in this project alone radioiodine has been used as a diagnostic tool in over 5,000 patients, and as a therapeutic agent in over 900

cases of hyperthyroidism and in about 75 cases of carcinoma of the thyroid.

Radioiodine is also used therapeutically by Dr. W. F. Greenwood to bring about a medical ablation of the thyroid in the occasional suitable patient with intractable angina pectoris. About one in three such patients has shown remarkable benefit from this treatment.

An application from Dr. Robert Sheppard of the Toronto Western Hospital for radioiodine to be used in the diagnosis and treatment of thyroid and associated endocrine disorders has been approved. A similar application from Dr. C. Ezrin for the use of radioiodine at Sunnybrook Hospital has been approved.

Radioiodinated human serum albumin has been used by Dr. Ramsey Gunton for studies of plasma volume. The metabolic turnover rate of gamma globulin and other fractions of the serum proteins by the use of specific fractions labelled or tagged with I^{131} is being carried out at Sunnybrook Hospital and also at the Toronto General Hospital. These studies have yielded some very interesting information about the turnover rate of gamma globulin in several patients suffering from the absence of gamma globulin from their serum or "agammaglobulinæmia."

RADIOACTIVE PHOSPHORUS, P^{32}

Radioactive phosphorus is also a very useful isotope and a whole series of investigations in which it is being employed are being carried out at a number of our centres. These investigations include:

1. The treatment and investigation of leukaemia, polycythæmia and other blood dyscrasias by Drs. K. J. R. Wightman, A. H. Squires and C. J. Bardawill.
2. The study of plasma phospholipid turnover in acromegaly and other conditions by Drs. K. J. R. Wightman, E. A. McCulloch and C. J. Bardawill.
3. The diagnosis and localization of brain tumours by Dr. T. P. Morley.
4. The diagnosis of eye tumours by Dr. G. A. Thompson.
5. The treatment of polycythæmia and multiple myeloma by Dr. J. G. Watt of the Toronto Western Hospital.
6. Studies in red cell and total blood volume by Dr. R. W. Gunton.

RADIOACTIVE CHROMIUM, Cr^{51}

Radioactive Cr^{51} in the form of the chromate is being employed by Dr. Wightman and his group in the study of red cell survival in various hæmolytic and other blood diseases, and red cells tagged by this isotope are also being used by Dr. Gunton in his red cell volume studies.

RADIOACTIVE GOLD

Radioactive gold solutions are being employed by Dr. C. L. Ash and his group in the treatment of malignant pleural and peritoneal effusions.

Dr. W. K. Kerr has begun his studies on the application of this isotope to the treatment of carcinoma of the prostate, and Dr. R. Mustard and his group are using radioactive gold in their study of lymphatic drainage.

RADIOACTIVE IRON, Fe^{59}

Dr. Dorothy Ley of the Western Hospital has already begun her studies on iron metabolism with radioactive Fe^{59} .

DISCUSSION

The diagnostic methods using radioactive iodine are now well-established techniques, and the simple uptake measurements which have been developed here may now be considered as routine rather than as investigational procedures. These measurements are, or will be very soon, carried on at the Toronto General Hospital, the Toronto Western Hospital, and Sunnybrook Hospital, D.V.A. Plans are in progress to do this at the Women's College Hospital as well. The I^{131} for non-cancer use is purchased by the individual hospitals, and patients are charged for this service. The isotope laboratory in Room 80 at the Banting Institute is still being used to receive the pooled shipments of radioactive iodine, and distribution is effected from there. Methods of treatment with both I^{131} and P^{32} are also well established, and many of the applications may now be considered as routine.

Of the investigations with phosphorus the detection of eye tumours with P^{32} is continuing, but rather slowly because of the small number of suitable cases. P^{32} and the brain Geiger probe are being used more and more frequently. Some of the results in this study have already been published by Dr. Morley.

The phospholipid turnover studies have been drawn up into a report which is to be submitted for publication.

Blood volume measurements with P^{32} in cases of heart failure have been reported recently in the *Journal of Clinical Investigation*. This paper appears to have been well received.

In conclusion, I would simply say that the work with isotopes is being vigorously continued and expanded, that their use is gradually spreading from the Toronto General Hospital to our other teaching hospitals, and that the work of the laboratory under the able direction of Dr. Paul is filling a very necessary and vital place in this program.

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(Information regarding contributions and advertising will
be found on the second page following the reading material.)

THE LAW AND ARTIFICIAL INSEMINATION

Anyone even remotely contemplating the practice of artificial insemination would be well advised to read with care the careful analysis of the legal aspects of this practice set out by Mr. Tallin, Dean of the Manitoba Law School, in the *Canadian Bar Review* for January and February 1956. Mr. Tallin mentions the three varieties of artificial insemination: (1) artificial insemination donor; (2) artificial insemination husband; (3) insemination with a mixture of semen from the husband and from another donor. This third variety he refers to as CAI (confused artificial insemination). His analysis is mainly concerned with the first and third groups.

Mr. Tallin is at no pains to conceal his manifest abhorrence for the practice of donor insemination, pointing out that there are serious social aspects to the practice. If it became widespread, it might well destroy family life as the basis of human society. If those who defend the practice allege that they can thereby relieve the supposed frustration of a comparatively few married and childless women, they should logically extend their solicitude to the equally deplorable plight of the unmarried woman or man or the married man denied the joys of parenthood by the incapacity of his wife.

The practice of donor insemination has apparently got itself into a vicious circle from which there is no escape. Because of the many legal angles associated with the practice, it has become necessary to carry it out with a great deal of secrecy. The very introduction of secrecy into the practice arouses suspicion of its honesty

and makes for fraud and deceit. Yet nothing can be done to alter this position unless both federal and provincial governments are prepared to enact extensive legislation (which Mr. Tallin sets out in detail) and no politician is likely to propose such legislation in the present state of public opinion.

Among the legal problems created by donor insemination, Mr. Tallin discusses in great detail the question of adultery and the illegitimacy of the product of such practices. There is no doubt in his mind that donor insemination constitutes in law adultery; this of course was the finding of the commission set up by the Archbishop of Canterbury in England to study the whole question several years ago. There is also no doubt in his mind that the child so conceived is illegitimate.

Physicians will be particularly interested in his remarks on their role in the practice of donor insemination. He says:

But, assuming that the man euphemistically described as the donor is in fact, as seems most generally to be the case, a mere vendor of semen, he would seem to be in a similar category to a prostitute, and the doctor morally, if not legally, in the same position as a common pimp or madam, or perhaps a person living on the avails of prostitution.

At least six categories of persons may be affected by the conduct of the physician, namely, the woman inseminated, her husband, the donor, the child produced, the next-of-kin of the woman and her husband, and any municipal corporation on whom the child might become a charge. In regard to the physician's relation to the woman inseminated, he will be held liable to produce as high a standard of care in this operation as in any other type of treatment, and he is therefore morally responsible for seeing that the spermatozoa injected are actually those of the donor. To accept the word of the latter would scarcely seem sufficient. Putting himself in the position of a vendor, there is an implied undertaking on the physician's part to see that the material used is fit for the purpose. Should some misfortune befall and the child be born, for example, an imbecile, or physically defective, the physician would be liable to be sued for damages resulting from the increased cost of caring for such an afflicted child. If the treatment should not be successful, the physician might be sued for a breach of contract. Should there be a leakage

and the name of the donor or recipient be discovered as a result of the physician's indiscretion, the door is open for blackmail and other unpleasant consequences.

There are several possibilities for legal action against the physician if he has inseminated a woman without her husband's consent. The donor may sue in the event that an affiliation order be made against him, or that he lose his position or his business or his wife because the part he played in insemination is discovered. Should the child, by reason of the neglect of its mother or of some mental or physical defect, become a charge on a municipality, the municipality might succeed in obtaining an order against the physician for the child's maintenance or an order compelling him to disclose the identity of the donor, so that the latter might be compelled to maintain the child. The doctor would not be protected from this disclosure by any claim of professional privilege.

Lastly Mr. Tallin discusses the criminal liability of the physician participating in this practice. On the assumption that the practice be held adulterous, the doctor might be convicted under the criminal code as a person conspiring with another to induce a woman to commit adultery. Furthermore, physicians are obliged to furnish information about births, including a description of the father. There are penalties for false certification. To quote Mr. Tallin:

"Could it be said that a physician, who artificially inseminated a woman with semen from a donor whose name is not known to her, has not formed with her a common intention of supplying false information for insertion in a register of births? Even though the primary purpose was to enable her to give birth to a child, yet the knowledge would still be present that the falsification of the register would be a probable consequence of carrying out the common purpose. Each of them would therefore be a party to the offence of falsifying the register."

After studying a long list of legal consequences ensuing upon donor insemination, only the boldest would venture upon this practice. Many will no doubt be approached with requests for donor insemination; nothing in the tradition of medicine obliges them to comply.

Editorial Comments

B.C.G. AND VOLE BACILLUS VACCINES

The recent therapeutic advances in the treatment of tuberculosis, and the earlier diagnosis and isolation of cases, bring into being a new problem with the increasing number of negative tuberculin reactors. Olsen,¹ in his recent report on the tuberculosis scheme in Bornholm, stresses the dangers of being tuberculin-negative. As far back as 1936, it was noted with alarm that the number of negative reactors among the population of the island was rising, and the Danes therefore introduced a scheme of B.C.G. vaccination for susceptible groups. Analyzing the results after nearly 20 years, Olsen comes to the conclusion that "... it is unfavourable to be tuberculin-negative; it is better to be naturally positive, but it is best of all to be B.C.G.-positive". In spite of the favourable results in Scandinavia, there is still disagreement in other countries as to the value of B.C.G. vaccination as a preventive of the disease. It is argued that no large-scale trial has hitherto been conducted in which there has been random selection of subjects and the inclusion of unvaccinated controls. Moreover Calmette's original claim that B.C.G. was a "virus fixe" has been refuted by many, and concern has been expressed about both the potential danger of a spontaneous restoration of virulence and of a progressive decrease in virulence to the point where it is incapable of acting as an efficient antigen. Killed tubercle bacilli have poor antigenic properties, as have naturally non-pathogenic strains such as *Mycobacterium phlei*, but in 1937 Wells² isolated a mycobacterium from the tuberculous lesions of wild voles and found it to have similar serological characteristics to human and bovine strains of tubercle bacillus but a low pathogenicity for other mammalian species. Numerous small-scale experiments have been carried out on both animals and humans to determine its value as an immunizing agent against virulent mycobacteria and have given, on the whole, favourable results.³⁻⁹ Wells⁹ found a high incidence of local post-vaccinal reactions following intracutaneous injection into humans, but with the multiple-puncture method of inoculation these reactions were no more frequent or severe than those following B.C.G. vaccination, and no generalized reactions resulted. The outstanding advantage of the vole bacillus over B.C.G. seems therefore to be that it does not require attenuation, being of a naturally suitable virulence for vaccination.

In 1949 the Medical Research Council of Great Britain appointed a special committee to plan and direct a large-scale trial of the relative efficacy of B.C.G. and vole bacillus vaccination in humans, and the first report of this Committee has recently been published.¹⁰ It is in the nature of a progress report, presenting

the results from a follow-up of over 50,000 children of school-leaving age over periods of not less than 2½ years. This age group was chosen for its naturally high incidence rate and mortality from tuberculosis, so that any benefit resulting from the vaccination would be more easily detected. For the same reason the trial was carried out in industrial urban areas in north London and the Midlands. All the children were volunteers, with their parents' consent, and were divided into three main groups of tuberculin-positive (40%), and vaccinated and unvaccinated negative reactors. In some areas the vaccinated groups were again divided, according to whether they were receiving B.C.G. or vole bacillus vaccine. The follow-up rate has been commendably high, 94% of the participants having been contacted during the 30 months following entry to the trial. Conversion to tuberculin positivity was obtained in approximately 99% of vaccinated cases and there was no essential difference between the two vaccines in this respect. In fact, the most important observation so far has been the marked protection afforded by inoculation with either. The annual incidence of tuberculosis in the vaccinated and originally tuberculin-negative groups has been one-fifth of that in the unvaccinated children. Protection would seem to be conferred within six months after immunization, and is still apparent after 2½ years.

Comparison of the vaccinated groups with the naturally tuberculin-positive reactors has shown that, while the case rates are similar in the vaccinated and those positive to 100 T.U., the children who were strongly positive to only 3 T.U. showed a higher incidence of tuberculous disease than even the unvaccinated negative reactors. It would seem therefore that in this age group those highly sensitive to tuberculin are particularly liable to develop tuberculosis.

Complications resulting from the vaccination were few and consisted only of local reactions at the vaccination site, with occasional regional lymphadenitis. The reactions appeared to be somewhat more frequent with vole bacillus vaccine, and the Committee is now investigating improved methods of inoculation.

The trial continues and future reports will give the results over longer periods of time, but, on the basis of the figures so far, it can be calculated that if all the tuberculin-negative and still uninfected entrants had been inoculated there would be an expected reduction of 55% in the total incidence of tuberculosis for the 2½ years.

Whether or not the vole bacillus vaccine will prove to have definite advantages over B.C.G. still remains to be seen and we must await the results of an extended trial, but in the face of existing evidence it is surely difficult to remain sceptical of the value of immunization in susceptible population groups.

ROSEMARY LINDAN

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DEATH BY MANIPULATION

In 1947 Pratt-Thomas and Berger¹ published an article on three cases in which death followed manipulation of the neck during chiropractic treatment. Recently Ford and Clark² of Baltimore have published an account of two cases in which injury to the central nervous system followed manipulation of the neck, and Schwarz of Philadelphia and his colleagues³ have added a third case. In the cases described by Ford and Clark the patient underwent a rotation of the neck and immediately became weak and dizzy and subsequently unconscious. In the more serious of the two cases, manipulation was actually performed by the patient's wife, who attempted to treat him for headache. She rotated his neck strongly to one side and he immediately staggered and fell. He appeared to be dazed, vertiginous and nauseated. He began to vomit and complained of loss of vision on his right side and noises in the right ear. His left arm was clumsy and he was unable even to sit up because he fell to the left. He died several days later in the Johns Hopkins Hospital, having meanwhile added a left hemiplegia to his disabilities. At autopsy, the basilar artery was found to contain two thrombi, and there were also thrombi in the left posterior cerebral artery and the left posterior inferior cerebellar artery. The other case reported by Ford and Clark was that of a man who immediately after chiropractic manipulation of his neck became unconscious, was taken to hospital where he vomited repeatedly, and recovered consciousness 24 hours later with paralysis of the left arm and leg and ataxia, together with dysphagia and dysphonia. When seen by the authors 10 years later he still had some neurological findings, including a hæmorrhage into the right retina, loss of function of the cervical sympathetic nerve tract on the right, cerebellar ataxia, sensation loss on the left side

of the face, body and left extremities, slight dysarthria and partial nerve deafness on the right side.

The patient reported by Schwarz and his colleagues was more fortunate. She became nauseated, weak and dizzy immediately after chiropractic manipulation of her neck for a head cold. She complained of blurring of vision in her right eye, had difficulty in swallowing and speech and on examination showed the classical neurological signs of injury to the posterior inferior cerebellar artery (Wallenberg's syndrome). However, within a few weeks she achieved almost complete recovery.

Ford and Clark speculate on the etiology of this condition. It is clear that such sudden injury to the brain must be due to interference with blood supply. Ford and Clark consider that the lesion is probably in the vertebral artery, and possibly at the joint between the axis and the atlas where rotation of the head chiefly occurs. Interference with vertebral artery blood flow presumably leads to secondary thrombosis higher up. Schwarz and his colleagues suggest that in such cases the diagnosis be made at an early stage and the patient treated with anticoagulants.

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EMIL KRAEPELIN (1856-1926)

This year marks the 100th anniversary of the birth of Emil Kraepelin, best known as the originator of the dementia præcox concept. He is also hailed as the "father of modern psychiatry" by some, and almost completely forgotten by others.

Kraepelin was born in Neu Strelitz, a small town in northern Germany, and raised under modest economic conditions. He developed an early interest in psychology through reading Wundt's books, and entered the study of medicine with the intention of becoming a psychiatrist. His first academic achievements after graduation were experimental studies on the influence of drugs and alcohol on mental functions. He became professor of psychiatry at the age of 30, teaching first in Dorpat (1886-1891), then in Heidelberg (1891-1903), finally in Munich

(1904-1922). It was during the Heidelberg period that he developed his system of psychiatric diagnostic classification. In Munich he organized the Research Institute of Psychiatry, still an active centre. In 1922 he retired from teaching to devote his entire time to the Research Institute. In his later years he became interested in the impact of racial characteristics on psychoses, and made extensive journeys. He also visited North America to compare general paralysis in the white races with that in Negroes and Indians. He died in 1926, working on the ninth edition of his textbook, and planning another research trip.

It has been said that psychiatry, "the oldest of the medical arts and the youngest of the medical sciences", was first established as a science around the turn of this century. During those eventful years Kraepelin contributed greatly to the fact that diagnosis in psychiatry became more than mere description. He developed a diagnostic system by longitudinal rather than cross-sectional observation of patient groups. His formula for creating nosological entities has been to define "disease" in psychiatry through common etiology, course, outcome and pathology. The concept of dementia præcox was first formulated by Kraepelin in the fourth edition of his textbook (1893). He defined it as an entity apart from the affective disorders, general paresis and other conditions. (The term "démence précoce", however, was used before by Morel with a different connotation.) Kraepelin himself was never quite satisfied with dementia præcox as a clear-cut entity. The definition of manic-depressive psychosis was another contribution by Kraepelin which still has a major impact on psychiatry. This nosological concept was added to the sixth edition of his textbook (1899). Kraepelin's rigidly compartmentalized approach to "disease" in psychiatry appears rather naïve today, and certainly outdated. But the entire scientific outlook in biology and medicine of Kraepelin's period—positivism in natural sciences, as inherited from the 19th century—was different and became outdated, yet his impact in psychiatry was and still is very considerable. His nosological classification created order in the terminological chaos of his period.

Much has changed since "the epoch of Kraepelin". The focus of interest in psychiatry has shifted away from the rigid generic principles towards the individual as part of his environment. Disease in psychiatry has become of syndrome or reaction form. Nevertheless the framework of diagnostic categories, although filled with new concepts, still shows the outline of the "Kraepelinian" system. A. BONKALO

Medical News in brief**HEROIC TREATMENT OF VERY SEVERE TETANUS**

Mollaret of Paris reports (*Deutsche med. Wchnschr.*, 81: 365, 1956) the results of treatment in four cases of severe tetanus by heroic methods. He employs curare products such as tubocurarine in doses sufficient to produce maximal curarization, i.e. complete disappearance of tetanic spasm, although clonic convulsions still occur at less frequent intervals. He also employs tracheostomy and artificial respiration with control of pressure variations by an Engström apparatus. He does not use general anaesthesia, and gives only small doses of agents which potentiate the action of curare. Three out of his four patients recovered, and he considers that no patient even with the most severe tetanus should now be considered in a hopeless condition.

SPONTANEOUS VARIATION OF BLOOD PRESSURE

It is very clear that if the blood pressure in normal individuals varies greatly from time to time, any effects of drugs on blood pressure must be interpreted with caution. Schroeder and Menhard of St. Louis (*Am. Heart J.*, 51: 577, 1956) now produce evidence from a study of both normal and hypertensive human subjects that there is considerable variation in arterial blood pressure. They recorded blood pressures directly by suitable intra-arterial manometers 112 times. They found that variations as great as 20-27 mm. Hg in systolic pressure and 12-19 mm. Hg diastolic pressure were observable; in normal subjects, however, variations were usually 10 mm. Hg or less. It is obvious that any single reading of blood pressure must be evaluated in terms of these variations. A single reading of blood pressure, even repeated several times, is accurate only within the limits of lability in the individual's vascular system.

VALVOTOMY FOR AORTIC STENOSIS

Drs. Baker and Campbell of Guy's Hospital, London, (*Lancet*, 1: 171, 1956) discuss the results of aortic valvotomy in 16 patients with aortic stenosis. They emphasize that this operation does not give such good results as valvotomy for mitral stenosis. Of the 16 patients they treated, six have died and only in five were good results obtained. Even among the latter, one patient died within 18 months. The main risk of the operation is production of aortic incompetence, because in advanced aortic disease the valve is calcified and deformed. They believe that valvotomy should be considered for children with congenital aortic stenosis if they have anginal pain or syncope on exertion, if signs of left ventricular strain are increasing, or if the heart is enlarging. In adults the only basis for assessing operability is the progressive increase in severe symptoms.

TORSION OF THE HEALTHY FALLOPIAN TUBE

From Paris (*Presse méd.*, 64: 559, 1956) Cordier and his colleagues report two cases of a gynaecological emergency which is seldom diagnosed before operation. In both cases they considered the diagnosis and in one it was made with certainty preoperatively. They refer to torsion of the healthy fallopian tube, which is distinguished by a number of cardinal signs and symptoms. These are attacks of acute pelvic pain with restlessness appearing at or around the time of the menstrual period, rapid pulse co-existing with an almost normal temperature, the presence of an extremely tender, irregular mobile mass at the side of the uterus, absence of pathognomonic signs of tubal pregnancy, and two particularly important signs—metrorrhagia and displacement of the uterus towards the side of the lesion. Treatment of this torsion is simple, either by salpingectomy or by hysterectomy if there are associated uterine lesions.

HYDROCORTISONE THERAPY OF CHRONIC MAXILLARY SINUSITIS IN CHILDREN

A group of Paris otolaryngologists (*Presse méd.*, 64: 530, 1956) have treated 19 cases of maxillary sinusitis in children by the injection of 60 mg. of hydrocortisone in solution into the maxillary sinus. They do this in the belief that sinusitis in small children is usually not an acute purulent process but an allergic condition. In 14 of their 19 cases the immediate results were excellent, as shown by the change in radiographic signs and also in the symptoms. In the other five, who were somewhat older children (age group 10-15), the method failed. Seven of the cured children were followed up for some time, and in four cases the cure was apparently permanent.

PROGNOSIS IN CARCINOMA OF COLON AND RECTUM

A series of 353 cases of carcinoma of the colon and rectum admitted to a Norwegian hospital in the past 22 years has been studied with special reference to prognosis (*Acta chir. scandinav.*, 110: 378, 1956). During this period of 22 years the operability rate has increased continually while operative mortality has decreased. For carcinoma of the colon a five-year survival rate after radical surgery is 54% and for carcinoma of the rectum 33.3%. Prognosis was better for right colon carcinomas than for left colon ones, and better for proximal than for distal rectal lesions. The microscopic appearance of the tumours and the presence or absence of metastases were great factors in prognosis. In both colon and rectum, a large tumour carried a better prognosis than a small one, which was frequently associated with metastases. It is curious to note that in colon carcinoma both resectability and five-year survival rates increased with increasing period of delay. The average delay in cured cases was longer than that for recurrent groups both in colon and rectal cases.

(Continued on advertising page 40)

PUBLIC RELATIONS FORUM

Conducted by L. W. HOLMES
Assistant Secretary, C.M.A.

XVII. A MEDICAL GRAND JURY

PATIENTS are sometimes dissatisfied with a doctor's services, or his fee, or some other aspect of medical care. These people seldom take these troubles to the doctor, however; they usually discuss them among friends and acquaintances, creating a serious medical public relations problem and undermining public confidence in the medical profession.

The approach to this problem is two-fold—preventive and corrective. The first seeks to prevent misunderstanding by developing public relations awareness among doctors, urging greater attention to the patient's physical and mental needs, and the discussion of the cost of medical care in advance of treatment. This aspect has already been covered in this series.

The second facet of the solution—corrective—is the grievance or mediation committee, set up by the medical society. This is the *medical grand jury* which hears patients' complaints about physicians' services and fees and attempts to reach an amicable and just settlement. It provides fair hearings for both patients and physicians whenever they are unable to resolve their disagreement.

The mediation committee helps the medical profession achieve its primary purpose—to bring the best possible medical care to the people—by (1) offering an efficient way of handling complaints; (2) protecting physicians by helping to settle complaints and preventing malpractice suits; and (3) demonstrating to the community that doctors have their patients' welfare at heart.

There are two types of mediation committees functioning in Canada today. In some provinces a single Divisional Committee serves. In others, Divisional and local branch society committees have been set up. The latter arrangement is the better. It provides a mediation service for small communities with few physicians, and at the same time may function as a "court of appeals" to which patients and physicians may take their complaints should local committees fail to settle them. It is obvious that the local committee can handle most complaints quickly and efficiently because committee members are usually acquainted with the local situation and the parties involved. Moreover, action of the local committee is of greater public relations value; it reveals the efficacy of local policing and self-disciplining by the doctors.

Physicians serving on mediation committees must be understanding, alert to the problems of both the public and the profession, and aware

of the importance of complete discretion. Doctor-members may be appointed by the society president or be elected by the membership. In some American grievance committees the immediate past president or the executive committee may be automatically appointed.

The appointment of lay members to the mediation committee is a debatable issue. No committee in Canada has yet taken this step. In the United States, however, some committees do have lay members. They argue that lay representatives, such as community leaders, business men and lawyers, enhance community trust in the effectiveness of a mediation committee since the public may feel that community representatives will maintain a more impartial attitude when hearing complaints than will a committee made up entirely of physicians.

Mediation committees may hear and handle three types of complaints: those involving individual society members, the society as a whole, or any physician in the locality regardless of whether he is a society member or not. The American Medical Association suggests that even though the society has no authority over non-members, most committees will wisely try to settle disputes between patients and these non-member physicians as a public relations gesture.

To be effective, a mediation committee must have some "persuasive" power. Without such power it may be viewed by the public as a "white-washing" mechanism for the profession.

The committee will accept complaints from patients, doctors or lay groups. Some committees will receive all complaints; some restrict the nature of such complaints to fees and emergency service; fees only; ethical questions. Fees, inadequate service and general misunderstanding are the most common causes of complaint.

An analysis of 40 cases handled by the Kings County (New York) Medical Society's mediation committee revealed the following cause of complaints: improper diagnosis or treatment (14); failure to explain costs (6); failure to make a call where patient knew doctor (6); overcharging (4); failure to give reports to patients on their conditions (3); failure to treat patient in an emergency (2); refusal to treat patient (2); patient not treated by doctor he expected (2); criticism of other doctor to patient (1); failure to follow up on patient's case (1); type of bill submitted (1); improper examination (1).

These figures indicate that though some complaints are based on actual medical service rendered by the physician, the majority of the trouble could have been eliminated if each doctor practised sound public relations as well as good medicine.

Some societies accept complaints in written form only and others will accept them in written form or by word of mouth. Having the complaint submitted by word of mouth initially can frequently give society officers receiving the complaint an opportunity to settle the disagreement before it goes to the mediation committee.

The committee should meet as required—although a periodic meeting, with or without com-

plaints to be reviewed, is recommended in the interest of keeping the purpose and activities of the committee before the members. Before meeting, the committee should urge the patient to talk over his dispute with the doctor. If no satisfactory agreement is reached in this first conference between patient and doctor, the committee must hear the dispute. Usually the committee hears the parties to the dispute separately.

Since a great many complaints coming before the mediation committee involve fees, fee determination is an important aspect of committee activity. A majority of American committees are authorized to determine a proper fee in given cases. A recent article in a popular publication points out that a California county medical society committee goes so far as to insist that the doctor accept the fee set by the committee. It *can* insist because the society will back the patient to the extent of providing witnesses and legal counsel should the doctor take the case to court. He seldom does!

Making the committee work effectively requires the full support of society membership and thorough information on its activities. Perhaps more important is the provision of adequate information to the public. Unless patients know of the existence of a mediation committee, they are not in a position to take advantage of it and will continue to work untold public relations harm by indiscriminate discussion.

Persuading doctors that the mediation committee should be publicized is the most difficult part of making the committee function properly. It has frequently been said that publicizing the committee will result in a flood of complaints, most of them from cranks. Experience in the United States would prove that wrong.

Telling the public about the formation of a committee must be followed up by periodic reminders. The initial announcement may be made through an advertisement or a news story. Most newspapers would be happy to have such an editorial feature. Repeat publicity can take the form of small ads in local papers, on radio and television. Repeat promotion can also be effected through the society's Speakers' Bureau and personal contact between doctor and patient.

There is also public relations value in making an occasional report on the activities of the mediation committee, without, of course, going into specific instances.

By justly handling disputes of a medical nature and rendering a fair decision, the mediation committee demonstrates to the public the desire of the medical profession to bring the best medical care to everyone and to serve the public interest.

GENERAL PRACTICE

GENERAL PRACTICE DEPARTMENTS IN HOSPITALS

*Prepared by the Committee on Hospitals
of the College of General Practice of
Canada.*



THE FAMILY is the basic unit of our modern society, and the family doctor is the basic unit of the medical profession. The competent general practitioner can provide good medical care for 85% of the

ills of people and knows when and where to obtain help for the remainder. It is desirable that the family doctor treat his patients as far as possible as he has the complete confidence of the family and knows their past history and their environmental problems.

If the family doctor is to measure up to these responsibilities it is essential that he have access to hospital facilities by being able to admit his patients to his neighbouring general hospital and treat them there according to his experience and training. The best way to integrate the family doctor into general hospitals that are large enough to be departmentalized is by the establishment of a Department of General Practice.

It is recommended that Departments of General Practice be established in all clinically well-departmentalized general hospitals including university affiliated hospitals whether privately or publicly owned.

The establishment and proper operation of a Department of General Practice can assure the family doctor his proper place in the hospital by providing him with:

1. Fair and equitable representation in all staff activities of the hospital.
2. Staff privileges to treat his patients within his competence and so improve the medical care of the patient.
3. Opportunities to participate in a continuous educational program.

GENERAL CONSIDERATIONS

1. Any action to create a Department of General Practice in a hospital should be initiated by the general practitioners practising in the community served by that hospital.
2. The Department of General Practice shall consist of physicians who do not limit their practice to a special field of medicine, surgery, or midwifery.
3. A fundamental principle to be accepted is that a Department of General Practice shall not function as a clinical service and patients shall not be admitted to this Department. Its responsibilities are administrative and educational. Each clinical service or department is responsible for the clinical care and treatment of patients.

The family doctor within his professional competence admits his patients to those departments such as medicine, surgery, obstetrics, or paediatrics and treats them within the rules and regulations of the department concerned. In establishing a Department of General Practice it is not the intention that it will infringe on the function of special departments.

4. The chief of the Department of General Practice shall be selected in the same manner as the chiefs of other departments. He shall be a member of the College of General Practice.

5. The members of the Department of General Practice should be encouraged to become members of the College of General Practice.

ORGANIZATION AND FUNCTIONS OF A DEPARTMENT OF GENERAL PRACTICE

Democratic representation is a basic concept of our way of life and should be carried into hospital administration.

The chief of the Department of General Practice as the representative of general practitioners shall be a member of the Medical Staff Advisory Committee. All standing and special committees such as Credentials, Records, Medical Audit, and Tissue Committees should include members of the Department of General Practice.

Where a general outpatient department has been established, it is recommended that the Department of General Practice have the responsibility of organizing, staffing and conducting this service and that all new patients should be seen first by a member of the Department of General Practice.

The care of indigent patients admitted through the outpatient department in a hospital shall become the responsibility of the service on which they are admitted. It is recommended that the physician who sees the patient in the outpatient department be permitted to admit, follow, and treat that patient under the supervision of the clinical department concerned.

A major function of this department is to assume responsibility for sharing in the educational activities of the hospital. Members of the Department of General Practice should take an active part in the presentation of cases and scientific papers at staff meetings, attend ward rounds of clinical departments, view autopsies and attend pathological conferences. In hospitals where there is a large Department of General Practice, scientific programs may be conducted within the Department and all members given an opportunity to accept the responsibility of making a personal contribution.

Members of the Department of General Practice should realize their special qualifications for participation in the training of interns, residents, and nurses, emphasizing at all times the close relationship between patient and doctor which the family physician understands and appreciates. It should be the special interest of the Department of General Practice to assist in the instruction of those interns who have signified a desire to train more intensively for general practice, and to encourage such interns to further their basic knowledge by taking another year of study in a General Practice Approved Residency.

To facilitate the training of practising physicians in specialty fields in which they wish to improve their knowledge and skills, it is recommended that the rules and regulations of the hospital provide for preceptorship training for them in the hospital. The staff should recognize the right of general practitioners to work under the direction of such preceptors. The extent of this preceptorship training shall be determined by each individual specialty service of the hospital in consultation with the Credentials Committee.

Part-time preceptorship may be provided if requested by members of the Department of General Practice for hospital interns who would benefit by association with the family doctor in his practice outside the hospital.

PROFESSIONAL PRIVILEGES OF GENERAL PRACTITIONERS

The accordance of staff membership or professional privileges in a hospital shall not be dependent upon certification or membership in special societies.

1. Privileges should be extended to all doctors to engage in the hospital in the practice of general medicine, paediatrics, obstetrics, and surgery, according to experience, judgment, and ability, as valued by the Credentials Committee.

2. Additional privileges should be granted through the Credentials Committee to those members of the General Practice Department who become qualified by training and experience to engage in more advanced work in a clinical service.

OTHER APPROVING ORGANIZATIONS

1. Joint Commission on Accreditation of Hospitals:

Standards for Hospital Accreditation—December 5, 1953.

"E. General Practice Department:

"A Department of General Practice shall be an organized segment of the medical staff comparable to that of other staff departments with the following limitations:

"1. The responsibilities of this department shall be limited to administration and education. It shall not be a clinical service and no patients shall be admitted to the department. If and when desirable, however, the department may be made responsible for conducting the outpatient clinic in whole or in part.

"2. Since the Department of General Practice will not have a separate service, the members of the General Practice Department shall have privileges in the clinical services of the other departments in accord with their experience and training, on recommendation of the Credentials Committee. In any service in which any general practitioner shall have privileges, he shall be subject to the rules of that service and subject to the jurisdiction of the chief of the clinical service involved."

In interpreting these regulations, Dr. Kenneth B. Babcock, Director, states:

"A general practice section in any hospital if functioning properly would be considered by our surveyors an attribute to the hospital more than anything else and no demerits are ever given for a section of general practice unless it is functioning improperly."

Dr. Babcock uses the term general practice section whereas in Canada we speak of the general practice department.

2. The Canadian Medical Association in its *Basis of Approval of Hospitals for the Training of Interns in Canada* recommends the following:

(a) "That Departments of General Practice be established where the size of the hospital and educational facilities make such an organization possible and feasible. Departments of General Practice are administrative rather than clinical in their organization and have been developed as a means of raising the status and prestige of general practitioners in the hospital. By belonging to such a department, practitioners may be attached to one or more clinical services in the hospital. This entitles them to attend ward rounds and be responsible for cases on such services. By these associations, general practitioners are able to obtain a more equitable status with other members of the medical staff and at the same time extend their professional competence and experience."

(b) "It is desirable that staff members in the Department of General Practice be members of the College of General Practice of Canada."

Committee on Hospitals,
DR. HAROLD M. TAYLOR (Chairman)
DR. D. E. HUNT, St. Catharines
DR. V. C. MALOWNEY, Toronto
DR. IRA POLLOCK, Toronto
DR. E. R. S. WYATT, Elmira.

ANNUAL GENERAL MEETING OF C.G.P.

The Annual General Meeting of the College of General Practice of Canada will be held during this convention on Thursday, June 14, in room 304 of the School of Commerce. The meeting will begin at 9 a.m. and will continue as long as necessary that day. Please mark this date on your calendar. We are planning an informative report on all our work. We want your help with a full discussion by you of all College activities. Bring your suggestions and problems.

We would like to meet you at our booth.

The Executive of the College will meet on:

Saturday, June 9: 1 p.m.—P.D.R. 3, Château Frontenac.

Friday, June 15: 9 a.m.—P.D.R. 3, Château Frontenac.

The Board of Representatives of the College will meet on:

Sunday, June 10: 9 a.m.—P.D.R. 4-7, Château Frontenac.

Monday, June 11: 9 a.m.—P.D.R. 4-7, Château Frontenac.

Tuesday, June 12 if necessary: P.D.R. 4-7, Château Frontenac.

MEDICAL ECONOMICS

NATIONAL HEALTH SERVICE IN AUSTRALIA

[We have been asked to furnish some details of the National Health Service in Australia, which has had much favourable publicity. The material which follows is based mainly on facts supplied by our sister organization in Australia.—ED.]

THE NATIONAL HEALTH SERVICE in Australia has now been in operation for several years. It is provided by the Federal (Commonwealth) Government under a specific part of the Commonwealth Constitution. The Service is divided into six parts: (a) National Tuberculosis Campaign; (b) Provision of free milk for school children; (c) Pharmaceutical Benefits; (d) Pensioner Medical Services; (e) Hospital Benefits; (f) Medical Benefits. We need not concern ourselves with the first two parts, the national tuberculosis campaign and the provision of free milk for school children, but may pass immediately to the last four sections.

The section headed "Pharmaceutical Benefits" is concerned with the free provision to every member of the community of drugs classifiable as either life-saving or disease-preventing or both. An official list has been compiled of 186 items, all single substances, which are considered to be either life-saving or disease-preventing. A contract has been arranged between the Government and registered pharmacists for the latter to supply at a fixed price to the Government and free of charge to patients all items on the official list. Items are obtained by prescription direct by doctors. There has been some criticism of this scheme in relation to the prescribing of antibiotics. At first a small percentage of the

profession indulged in indiscriminate prescribing of these costly drugs, but arrangements have now been worked out by co-operation between the profession and the Government to solve this problem. A list of specific diseases for which antibiotics are indicated is now available, and doctors are required to observe this. The scheme has of course led to an increase in the amount of clerical work done by practitioners. However, it seems that the Service is logical from the patient's and the Government's point of view, while it preserves the doctor's freedom and discretion in prescribing as well as the pharmacist's freedom and economic status. Analysis of expenditure on major drug items shows that antibiotics cost 47% of the whole. The number of prescriptions has gradually risen since the scheme began in 1951 from 6,500,000 to 9,268,000.

FREE MEDICAL SERVICE AND MEDICINES TO PENSIONERS

The pensioner medical service began in 1951 and was designed to provide general practitioner services free of charge to all persons in receipt of an age, invalid, widow's or service pension, and their dependants. It was later extended to include special pharmaceutical benefits. The scheme is based on fee-for-service, the patient signing a voucher on each occasion when he visits the doctor and the doctor claiming payment from this voucher. Any practitioner may participate in the service and he may charge a pensioner patient a small fee for undue distances on house calls or for service after hours. The number of persons covered in 1955 was 640,000. The number of doctors participating was 4,500, and they each received an average payment of roughly \$1,500 a year. The consultation charges are based on two-thirds of the usual private charge. Medicines which may be prescribed free include all the regular pharmacopoeial drugs plus some others.

It has been suggested that this pensioner medical service has been abused, and certainly the number of services per individual member rose each year until recently by a surprising amount. Abuse on the part of the profession is limited to a very small section, about 2%, and the rest of the profession is taking active steps to control these very few unruly members. Abuse by patients is, of course, much more difficult to control and presumably fairly widespread.

HOSPITAL BENEFITS

The hospital benefits section of the National Health Service began in 1952 and is based on the principle of subsidizing benefits received by way of contribution to voluntary insurance organizations. Any person who has taken the trouble to insure himself with a voluntary

organization receives, therefore, not only a grant from his voluntary organization while in hospital, but also a grant from the Federal Government which usually amounts to twice the voluntary grant. The scheme has placed public hospitals on a sound basis. Whereas, before its introduction, hospitals were deeply in debt and working on large overdrafts, the situation has now changed and some hospitals even have a surplus. The percentage of the population covered in this way is 56%, making a total of some 5 million members.

MEDICAL BENEFITS

The medical benefits scheme came into operation on July 1, 1953, and is based on the same principle as the hospital benefits scheme. In other words, persons who voluntarily insure themselves receive, in addition to the benefits their insurance society gives, a State contribution towards the cost of their medical care. Administrative costs of the scheme are borne mainly by the voluntary organizations themselves and there are two schedules of benefits. The first schedule covers some 120 items of service usually rendered by a general practitioner; the second schedule contains 288 items usually rendered by specialists, such as radiologists, pathologists, surgeons, etc. The voluntary organizations recognized must be non-profit-making and they are required to at least match the Federal benefit which ranges from 6 shillings (roughly 90 cents) for a consultation (the usual fee for private office calls is 15 shillings) to about £12 for an operation. When the patient is referred by a general practitioner to a specialist, the Federal Government pays a benefit for the consultation and the voluntary organization pays at least an equivalent amount.

There are several hundred voluntary insurance organizations, the largest being the Medical Benefits Fund of Australia, which was established by the medical profession in 1947 when it was threatened with nationalization. The Medical Benefits Fund has 600,000 members and covers approximately 1,300,000 persons out of a total population of over 9 million.

The Medical Benefits scheme has met with several criticisms. The first is its failure to cover pre-existing disease. However, such persons may now be paid benefits after two years of membership. A time-lag in payment of benefits was also a source of irritation, but this is now being wiped out. The third criticism is that the amount of the doctor's bill which is covered by Government and voluntary organization insurance varies greatly from service to service. In some cases it approaches 90% (the maximum allowed by law) whereas in others it covers only 40% of the bill. It is anticipated that in due course the Government and the organizations will be able to work out a more equitable repayment scheme. Forty-five per cent of the population

is covered by this scheme, and the total costs in 1955 were roughly met as to one-third by Fund benefit, one-third by Federal benefit and one-third out of the insured member's pocket.

It is thought that the medical profession is very happy with the scheme, for it conserves all the principles for which it has fought over the years. Professional freedom is guaranteed, the doctor-patient relationship is not altered, and an economic foundation for medical practice has been laid down.

MEDICAL MEETINGS

CANADIAN UROLOGICAL ASSOCIATION

The 12th annual meeting of the Canadian Urological Association will be held on June 7, 8 and 9 at the Alpine Inn, Ste. Marguerite, Quebec. This resort is located on the banks of the North River in the Laurentians, 52 miles north of Montreal. The meeting is so timed that members will be able to participate in the annual C.M.A. meeting at Quebec afterwards. A social program has been worked out, including special events for the ladies and a variety of entertainments—a golf tournament, fashion shows, fishing, dancing and a demonstration of Quebec handicraft. The annual meeting of the Executive will take place on Wednesday, June 6 at 6:00 p.m. and the annual meeting of the Association will be held on Friday, June 8 at 12:00 noon.

The following is a provisional scientific program:

June 7.—Malignant Testis Tumours in Children, M. Siminovitch, Montreal; Urinary Frequency in the Female, W. E. Ortved, Toronto; Acid-Base Balance and Fluid Management, E. H. Bensley (by invitation), Associate Professor of Public Health and Social Medicine, McGill University; The Ileum as a Substitute Bladder, Eugene M. Bricker (by invitation), Barnes Hospital, Saint Louis, Mo.

June 8.—Bilateral Ureteral Obstruction due to Retroperitoneal Fibrosis, Lloyd McAninch, London, Ont.; Experimental Urolithiasis and Hyaluronidase, L. Reese, London, Ont.; Urological Complications in Poliomyelitis, J. Reid Taylor, Winnipeg; Harris Prostatectomy, J. H. McBeath, Winnipeg; Vesical Atony Following Prostatectomy; a review of treatment including partial cystectomy, James M. Campbell, Saskatoon; Bladder Denervation, J. P. Bourque, Montreal; Annual Meeting, Introduction of Incoming President.

June 9.—Uretero-Intestinal Transplant, An Experimental Study, C. M. Allen (by invitation), Montreal; Bladder Carcinoma, W. F. Whitmore, Jr. (by invitation), New York City; Changing Concepts in the Management of Primary Bladder Tumours, W. E. Collins, Ottawa; Modern Radio-Therapeutic Approach to Bladder Tumours, A. R. Catton (by invitation), Ottawa.

Information may be obtained from David Swartz, Secretary, 332 Medical Arts Bldg., Winnipeg.

CANADIAN CANCER SOCIETY

The 1956 annual meeting of the Canadian Cancer Society will be held in the Château Frontenac, Quebec City, on Thursday, May 31, 1956, at 11 a.m., to receive the reports of the directors and the auditors and to transact other business.

CANADIAN ANÆSTHETISTS' SOCIETY

The Annual Meeting of the Canadian Anæsthetists' Society will be held at Mont Tremblant Lodge, Mont Tremblant, P.Q., June 18-20, 1956. The program follows:

Monday, June 18: Afternoon Session: Comparative Evaluation of Dolitron in Human Volunteers—Dr. Gordon Wyant, Saskatoon; Clinical Evaluation of Viadril—Dr. R. A. Gordon, Toronto; Evaluation of a New Hibernizing Drug from Dibenzothiazine—Dr. Gérard Mignault, Montreal; Ethyl Vinyl Ether—Dr. Doris Crosskreutz, Chapel Hill, N.C. The Council will meet at 8 p.m.

Tuesday, June 19: Morning Session: An Evaluation of Local and General Anæsthesia for Bronchoscopy—Dr. H. B. F. Fairley, Toronto; Postoperative Care of Thoracic Surgical Patients—Dr. James G. Robson, Montreal; Cortisone and Anæsthesia—Prof. Hans Selye, Montreal; Pulmonary Function Tests—Dr. Fernand Grégoire, Montreal. *Afternoon Session:* Experience with Hypothermia at the Toronto General Hospital—Dr. S. M. Campbell, Toronto; Anæsthetic Aspect of Thymectomy for Myasthenia Gravis—Dr. Jone Chang, Vancouver; The Use of Trifluoroethyl Vinyl Ether (Fluoromar) in Anæsthesia for Dentistry—Dr. H. M. Slater, Montreal; Pre-tonal, A Short-Acting Muscle Relaxant—Dr. Harold Griffith and Dr. Peter Welt, Montreal.

Wednesday, June 20: 9 a.m., Round Table, Anæsthesia for Cæsarean Section; Chairman, Dr. Alan Noble, Montreal; Members, Dr. Elizabeth Martin, Rochester, N.Y., Dr. John Carroll, Vancouver, and Dr. David Power, Montreal. 10.30 a.m., Annual General Meeting. *Afternoon Session:* The Clinical Use of Neraval—Dr. Ralph Tovell, Hartford, Conn.; Artificial Heart-Lung Apparatus (Three Years' Experience in Dogs)—Dr. Jean-Louis Tremblay, Quebec City; Round Table, Questions Submitted during the Meeting, Dr. John Carroll, Vancouver, Chairman. Council will meet at 5 p.m., and the Annual Dinner will be held at 8 p.m.

CANADIAN HEART ASSOCIATION

The program for the ninth annual meeting of the Canadian Heart Association, to be held in Quebec City on June 14 and 15, is as follows.

June 14.—Round Table Conference (jointly with the Canadian Medical Association), Indications for the Surgical Treatment of Heart Disease, J. H. Palmer, M.D. (Chairman), Montreal, Paul David, M.D., Montreal, W. G. Bigelow, M.D., Toronto, R. S. Fraser, M.D., Edmonton, and Arnold Johnson, M.D., Montreal; The Fate of the Implanted Mammary Artery in Human Ischaemic Hearts with a Study of Clinical Results in Fifty Cases, G. C. McMillan, M.D., and Arthur Vineberg, M.D., Montreal; Recognition and Treatment of Patent Ductus Arteriosus Complicated by Pulmonary Hypertension, David R. Murphy, M.D., and Gordon Karn, M.D. Montreal; Subtotal Pericardiectomy for Constrictive Pericarditis, W. G. Bigelow, M.D., D. R. Wilson, M.D., F. G. Dolan, M.D., and R. W. Gunton, M.D., Toronto; The Closure of Interauricular Septal Defects under Hypothermia, Experimental Study, J. A. Gravel, M.D., Quebec City; Aldosterone and Human Hypertension, Jacques Genest, M.D., Montreal; Abnormality of Cestrogen Metabolism in Men with Coronary Artery Disease, W. S. Bauld, M.D., Ian Milne, M.D., and N. Givern, B.Sc., Montreal; Transaminase Activity in Myocardial Infarction, André Proulx, M.D., Jacques Gauthier, M.D., and Jean-Marc Bordeleau, M.D., Montreal; General Systemic Effects and Electrocardiographic Changes Following Injections of Digitalis Glycosides into the Lateral Ventricle of the Brain, H. E. Shister, M.D., and K. I. Melville, M.D., Montreal; Apical Systolic

Murmur and Mitral Stenosis, Osman Gialloredo, M.D., Maurice Barbezat, M.D., and Paul David, M.D., Montreal; Pericarditis, John Merriman, M.D., Saskatoon; The Use of the Master Test in the Diagnosis of Angina Pectoris in Office Practice, Richard Lessard, M.D., and Georges Saulnier, M.D., Quebec City.
June 15.—Business Meeting.

INDUSTRIAL MEDICINE

The annual combined meeting of the Industrial Section of the Ontario Medical Association and the Industrial Medical Association of the Province of Quebec will take place in Hamilton, Ontario, on September 26, 27, and 28, 1956.

All physicians with full or part-time industrial affiliations are welcome to attend this most interesting, informative, and pleasant program. Registration will be at the Royal Connaught Hotel from 9.00 to 11.00 a.m. on September 26, 1956.

CANADIAN RHEUMATISM ASSOCIATION

The Annual Meeting of the Canadian Rheumatism Association will be held in conjunction with the Annual Meeting of the Canadian Medical Association, in Room 312 of the Ecole de Commerce, Quebec City, on Thursday and Friday, June 14 and 15. The preliminary program follows:

Thursday, June 14

Morning Session: Serum Mucoproteins and Electrophoretic Patterns in Rheumatic Diseases—Kenneth R. Mackenzie, Louis G. Johnson and Cooper H. Stacey, Montreal. The Distribution of Serum Uric Acid and Some Observations on the Activity of Uricase—Jeffrey E. Morris, Winnipeg. Nature and Origin of Fibrinoid in Subcutaneous Nodules of Rheumatic Fever and Rheumatoid Arthritis—Henry Z. Movat and Robert H. More, Kingston (by invitation). Antistreptolysin-O Titres in Normal Young Adults and in Diseases—Maurice Saint-Martin, Montreal (by invitation). Council Meeting (11.30 a.m.).

Afternoon Session: Observations on Conjugated and Unconjugated Steroids in Human Blood—Marvin Darrock, Vancouver (by invitation). Stress and the Rheumatic Diseases—Hans Selye, Pierre Bois and Gaetan Jasmin, Montreal (by invitation). Rheumatic Manifestations in Hodgkin's Disease, Leukæmia and Allied Conditions—Edmond Paquet and Jean-Marie Delage, Quebec (by invitation). Interrelationship of the Various Tests for the "Specific" Rheumatoid Arthritis Factor—Ronald W. Lamont-Havers, New York. Vertebral Lipping—Ian Macnab, Toronto. Use of Hydrocortisone in the Treatment of the Painful Shoulder (film)—Arthur W. Bagnall, Vancouver.

Friday, June 15

Morning Session: Hypersensitivity Reactions to Cortisone and its Analogues—Arthur W. Bagnall, Vancouver. Treatment Results in a Rehabilitation Centre for Rheumatic Disease—Harold S. Robinson, Vancouver. Prevention and Correction of Deformity of the Knee in Arthritis—Roger Gariépy, Montreal. Rheumatoid Nodules in Marie-Strümpell Spondylitis—Hugh A. Smythe, Toronto. Multiple Myeloma; Presenting Symptoms and Course—John R. Martin, Montreal. Some Aspects of Infectious Arthritis—Simon Dworkin, Louis G. Johnson and Kenneth R. Mackenzie, Montreal.

Afternoon Session: The Psychologic Factor in Rheumatoid Arthritis—Albert W. Grokeest, New York (by

invitation). Report: First Pan-American Congress—Arthur W. Bagnall, Vancouver. Report: Third European Congress—L. P. Mantha, Ottawa. Annual General Meeting (3.45 p.m.).

SYMPOSIUM ON HYPOTENSIVE DRUGS

(From a special correspondent)

Under the auspices of the Biological Council a symposium on hypotensive drugs and the control of vascular tone was held in London, England, on April 5 and 6. It was opened by Sir Charles Harington. In the clinical section most speakers said that they preferred to use two drugs in combination, usually a ganglionic blocking agent, and one of the rauwolfia alkaloids, or hydralazine. Professor J. McMichael (London) gave the results of five years' treatment of patients having malignant hypertension with ganglionic blocking agents such as hexamethonium, and pentolinium, combined with reserpine. Pentolinium, which was the drug he favoured, was given by injection twice a day, a double dose being given at night to minimize side-effects. The oral use of ganglionic blocking agents has been abandoned because of paralytic ileus and "methonium lung". Of 73 patients with grade IV malignant hypertension (Keith-Wagener classification), the five-year survival rate was 50%; in a control untreated group most patients were dead after 2½ years. The prognosis was not good in patients with a blood urea of more than 60 mg. per 100 ml. Following reduction in blood pressure, heart failure, retinitis, and headache rapidly disappeared, but papilloedema took many months to clear. Gross cerebrovascular complications and the risk of thrombosis and hæmorrhage remained unaffected. McMichael said that he was careful not to drop the blood pressure too low, otherwise angina and cardiac infarction might occur.

Professor F. Smirk (Dunedin, New Zealand) confirmed that the expectation of life was related to the control of blood pressure. He liked to keep it in the region of 110 to 140 mm. systolic, measured standing, and he took full advantage of the standing or sitting position to enhance the fall in blood pressure. During the last 18 months, treatment had been with pentolinium given subcutaneously and one of the rauwolfia alkaloids, such as reserpine, rescinnamine or canescine in doses of 0.5 to 1 mg. daily respectively. Over a period of six years the survival rate in patients with malignant hypertension, group IV, was 57%; in untreated cases of similar severity it was 2%. The over-all survival figure in 320 patients with all grades of malignant hypertension during the last six years was 75%. Professor Smirk said that many cases with heart failure and cardiac asthma cleared up with pentolinium and rauwolfia alkaloids, without the usual orthodox treatment. He encouraged all patients to inject themselves twice a day with a ganglionic blocking agent. Professor Smirk did not favour the use of ecolid and mecamlamine, as they caused a feeling of malaise and too many side-effects.

Results obtained in Sweden were described by Dr. B. Hood (Gothenburg) who said that he and his colleagues had treated 900 patients in the last 5½ years with ganglionic blocking agents. Of grade III cases 50% survived for five years or more. In a small series of 66 malignant hypertensives of grades III and IV treated with pentolinium and either one of the rauwolfia alkaloids or hydralazine, 55 were still living, of whom 36 were in full-time employment. Dr. Lockett (London) described promising clinical trials on some new ganglionic blocking agents derived from diquaternary-amino-benzhydryl compounds. They had a potent, prolonged action, were active by mouth, and had minimal side-effects on the mouth, eye and gut.

Dr. G. Perera (New York) was not so enthusiastic about the use of hypotensive drugs in either malignant

or non-malignant hypertension. The rauwolfia alkaloids not only failed to reduce the blood pressure adequately, but they produced mental depression, and the veratrum alkaloids had to be given in emetic doses before they had any effect.

Pentolinium and the other ganglionic blocking drugs ameliorated symptoms, and relieved retinopathy and congestive failure more effectively than rest or sedation. But side-effects and difficulties of administration precluded their use in all but co-operative patients with advanced disease. Dr. Perera said that the lives of many patients with symptomless hypertension were being made miserable by the administration of these potent drugs.

In the session on the chemical and biochemical aspects of the hypotensive drugs, Dr. H. Ing (Oxford) summarized what was known on their structure-activity relationships. There were still big gaps in our knowledge, he said. What was wanted was an orally active compound producing mainly a sympathetic block, and with little or preferably no action on the parasympathetic. Dr. Blaschko (Oxford) discussed the role of serotonin and amine oxidase as possible regulators of blood pressure. He traced the probable transformation of tyrosine in the body to "dopa", "dopamine" (dihydroxyphenylethylamine), noradrenaline and adrenaline.

In the pharmacology session, Dr. Marthe Vogt (Edinburgh) spoke on the mode of action of reserpine, which, she said, acted centrally, possibly through the posterior hypothalamus. There was evidence that it acted by releasing serotonin (5-hydroxytryptamine), from platelets and the bowel and brain. All the rauwolfia alkaloids with a tranquillizing action released serotonin, which had a depressor affect. Dr. J. C. Widdicombe (London) dealt with the pharmacology of the veratrum alkaloids, the action of which in man is still unknown. In the animal they produce hypotension, bradycardia, and transient apnoea. The ganglionic blocking drugs were described by Dr. Elenor Zaimis (London) who with Paton introduced them into medicine. She referred to the prolonged action of ecolid and mecamlamine, the latter being chemically unique as it was a secondary amine and the first non-quaternary ammonium compound to show a powerful ganglionic blocking action.

At the session on the vascular control of hypertension Professor Clifford Wilson (London) said that the lesions in malignant hypertension might be due to changes in vascular tone, especially in the brain, retina and kidney. A regional vasoconstriction might lead to fibrinoid necrosis of the arterioles. Dr. B. Folkow (Gothenburg) considered hæmodynamics of hypertension. If the internal diameter of a blood vessel were decreased by as little as 5% owing to thickening of the wall, he had calculated that resistance to blood flow would be increased by 20%. Slight structural changes might produce hæmodynamic effects long before they could be detected histologically.

WORLD MEDICAL ASSOCIATION

The 26th Session of the Council of the World Medical Association was held in Cologne, Germany, April 29 to May 5, to implement decisions taken at the 9th General Assembly and to prepare for the 10th Assembly in Havana, Cuba, October 9-15, 1956.

On May 1 the Secretariat of the World Medical Association moved its offices to the newly opened Coliseum Tower Office Building at 10 Columbus Circle, New York 19, N.Y. The Coliseum is, of course, the new gigantic convention and office building which is so large that it offers facilities for three different simultaneous conventions on its premises. The American Medical Association intends to hold its annual meeting there in June 1957.

SCIENTIFIC PROGRAM

EIGHTY-NINTH ANNUAL MEETING

Canadian Medical Association

QUEBEC, JUNE 11-15, 1956

Arrangements for the 89th Annual Meeting have been completed and a very attractive program of business, scientific and social activities has been prepared. In addition to the meeting of The Canadian Medical Association, a number of affiliated specialist societies have arranged to hold their annual meetings in close relationship.

The General Council of The Canadian Medical Association will meet on Monday and Tuesday, June 11 and 12, in the Ballroom of the Château Frontenac.

The scientific program will be presented on Wednesday, Thursday and Friday, June 13, 14 and 15, all sessions being held in the School of Commerce, Laval University. The scientific program follows:

Wednesday, June 13

ROUND TABLE CONFERENCES

9.00 a.m. - 10.15 a.m.

External and Internal Fixation of Fractures

DR. J. ANTONIO SAMSON, Montreal (*Chairman*)
DR. J. GORDON PETRIE, Montreal
DR. DAVID L. MACINTOSH, Toronto
DR. EDGAR LEPINE, Montreal
DR. J. A. LÉO WALKER, Montreal
DR. ROGER GARIÉPY, Montreal

Obstetrical Hæmorrhage

DR. LÉON GÉRIN-LAJOIE, Montreal (*Chairman*)
DR. GEORGE M. WHITE, Saint John
DR. RENÉ SIMARD, Quebec
DR. BRIAN D. BEST, Winnipeg
DR. W. D. MARSHALL, Victoria

Anticoagulant Therapy

DR. IRWIN M. HILLIARD, Saskatoon (*Chairman*)
DR. DONALD LLOYD-SMITH, Montreal
DR. LEO LONG, Montreal
DR. A. J. KERWIN, Toronto
DR. BEVERLY LYNN, Saskatoon

Rehabilitation of the Hemiplegic

DR. GUSTAVE GINGRAS, Montreal (*Chairman*)
DR. A. T. JOUSSE, Toronto
DR. ROGER DUFRESNE, Montreal
DR. E. D. WITTKOWER, Montreal
DR. CLAUDE BERTRAND, Montreal
DR. K. C. CHARRON, Ottawa

GENERAL SESSION

10.30 a.m. - 12.15 p.m.

DR. T. C. ROUTLEY (*Chairman*)

The President's Valedictory Address

DR. T. C. ROUTLEY, Toronto

As You Look—So Shall They See

DR. P. ROBB McDONALD, Philadelphia

The Osler Oration—Actual Orientation of Research on the Etiology of Pulmonary Tumours

DR. ANTOINE LACASSAGNE, Paris

SESSION A

2.00 p.m. - 5.00 p.m.

DR. WALTER DE M. SCRIVER, Montreal (*Chairman*)

The Management of Arterial Hypertension

DR. JACQUES GENEST, Montreal

Heart Failure in Infants and Children

DR. JOHN KEITH, Toronto

Cardiac Metastases in Bronchogenic Carcinoma

DR. GUY DROUIN, Quebec

Clues in the Diagnosis of Curable or Reversible Cardiovascular Disease

DR. FRANKLIN BERKMAN, Ottawa

The Operative Treatment of Coronary Disease

DR. W. H. PHILIP HILL, Montreal

SESSION B

2.00 p.m. - 5.00 p.m.

DR. FRANÇOIS ROY, Quebec (*Chairman*)

Radiological Diagnosis of Lesions of the Œsophagus

DR. ALBERT JUTRAS, Montreal

Benign Lesions of the Œsophagus

DR. JACQUES TURCOT, Quebec

Hiatus Hernia and Œsophagitis

DR. VICTOR O. MADER, Halifax

Œsophageal Varices

DR. S. JAMESON MARTIN, Montreal

Surgical Treatment of Carcinoma of the Œsophagus

DR. ROSS ROBERTSON, Vancouver

Œsophageal Diverticula

DR. R. A. MUSTARD, Toronto

SECTION OF OBSTETRICS AND GYNÆCOLOGY

2.00 p.m. - 5.00 p.m.

DR. JEAN DE SAINT-VICTOR, Quebec (*Chairman*)

A Plan of Management of Abruption Placentæ

DR. GORDON W. PRUETER, London

Some Problems in Paediatric Gynaecology
DR. FRED E. BRYANS, Vancouver

Infection in the Newborn
DR. A. J. DePAPE, Winnipeg

The Management of Anoxia in the Newborn
DR. JOHN MANN, Toronto

Thursday, June 14
ROUND TABLE CONFERENCES

9.00 a.m. - 10.15 a.m.

Questions and Answers in Paediatric Dermatology
DR. EMILE GAUMOND, Quebec (*Chairman*)
DR. NORMAN WRONG, Toronto
DR. A. R. BIRT, Winnipeg
DR. GEORGES LECLERC, Montreal
DR. D. R. S. HOWELL, Halifax

Indications for the Surgical Treatment of Heart Disease
DR. J. H. PALMER, Montreal (*Chairman*)
DR. PAUL DAVID, Montreal
DR. W. G. BIGELOW, Toronto
DR. R. S. FRASER, Edmonton
DR. ARNOLD JOHNSON, Montreal

Eye Emergencies
DR. ROLAND VIGER, Montreal (*Chairman*)

The Recognition and Management of Psychiatric Emergencies
DR. C. A. MARTIN, Quebec (*Chairman*)
DR. ROBERT O. JONES, Halifax
DR. ELLIOTT EMANUEL, Montreal

GENERAL SESSION

10.30 a.m. - 12.15 p.m.

DR. C. A. GAUTHIER, Quebec (*Chairman*)
The Tisdall Oration—Unconsidered Mechanisms Involved in Maintaining the Stability of the Internal Environment
DR. R. A. McCANCE, Cambridge

Vaccination Against Poliomyelitis—Some Basic Principles in Canada
DR. A. J. RHODES, Toronto

Problems of Staphylococcal Infections
SIR HOWARD FLOREY, Oxford

SESSION A

2.00 p.m. - 5.00 p.m.

DR. E. S. MILLS, Westmount (*Chairman*)
Carbon Tetrachloride—An Underrated Hazard
DR. GUY E. JORON, Montreal

Some New Findings Concerning the Prevention of Tuberculosis
DR. HUGH E. BURKE, Montreal

The Diagnosis and Treatment of the Menopause
DR. MARION HILLIARD, Toronto

The Treatment of Thyroid Disease by Radioactive Isotopes
DR. CHARLES H. JAIME, Hamilton

The Nervous Manifestations of Porphyria
DR. RAYMOND GARCIN, Paris

SESSION B

2.00 p.m. - 5.00 p.m.

Five Hundred Cases of Pulmonary Resection for Tuberculosis

DR. JEAN M. LEMIEUX, Quebec

Surgical Advances in the Relief of Leg Ischaemia
DR. J. C. LUKE, Montreal

The Diabetic Foot
DR. ANGUS D. MCLACHLIN, London

Aortic Aneurysms, With and Without Surgery
DR. W. G. BIGELOW, Toronto

An Evaluation of Surgical Procedures in Peptic Ulcer
DR. WILFRID M. CARON, Quebec

SECTION ON MEDICAL CARE

2.00 p.m. - 4.30 p.m.

DR. C. A. GAUTHIER, Quebec (*Chairman*)
A Study of Medical Care under Windsor Medical Services
DR. S. J. AXELROD, Ann Arbor

Universal Hospital Care in Saskatchewan
DR. BURNS ROTH, Regina

The Provision of Hospital and Ambulatory Services in Radiology and Laboratory Medicine
DR. F. W. JACKSON, Ottawa

ARMED FORCES MEDICAL SECTION

2.00 p.m. - 5.00 p.m.

DR. J. L. LAROCHELLE, Quebec (*Chairman*)
Medical Aspects of Maritime Arctic Operations
SURGEON LIEUTENANT D. J. KIDD, R.C.N., Halifax

Medical Services in Cold Weather Warfare
MAJOR J. E. GILBERT, R.C.A.M.C., Ottawa

Medical Aspects of Military Operations by the R.C.A.F. in a Cold Climate
SQUADRON LEADER L. A. WRIGHT, R.C.A.F., Ottawa

Some Physiological Aspects of Arctic Warfare
DR. J. A. HILDES, D.R.B., Winnipeg

Friday, June 15

ROUND TABLE CONFERENCES

9.00 a.m. - 10.15 a.m.

Reactions to the Administration of Antitetanic Serum
DR. OWEN V. GRAY, Toronto (*Chairman*)
DR. J. D. L. FITZGERALD, Toronto
DR. R. J. WILSON, Toronto
DR. JACQUES LEGER, Montreal

Problems of Tonsillectomy
DR. J. C. RATHBUN, London (*Chairman*)
DR. A. W. BAGNALL, Vancouver
DR. H. L. BACAL, Montreal
DR. ROLAND LAVOIE, Quebec
DR. CARL C. STODDARD, Halifax

The Medical Aspects of Traffic Accidents
DR. HAROLD ELLIOTT, Montreal (*Chairman*)

The Treatment of Soft Tissue Wounds
DR. GEORGES CLOUTIER, Montreal (*Chairman*)

GENERAL SESSION

10.30 a.m. - 12.15 p.m.

DR. J. R. LEMIEUX, Quebec (*Chairman*)**Ulcerative Colitis**

DR. LAWRENCE S. FALLIS, Detroit

Industrial Medicine: A New Specialty

DR. W. P. SHEPARD, New York

Chronic Bronchitis and Emphysema

DR. RONALD V. CHRISTIE, Montreal

SESSION A

2.00 p.m. - 4.30 p.m.

DR. RICHARD LESSARD, Quebec (*Chairman*)**The Treatment of Nervous Depression**

DR. JEAN SAUCIER, Montreal

The Uses and Abuses of Chlorpromazine

DR. LENNOX BELL, Winnipeg

The Restoration of Electrolyte and Fluid Balance in Vomiting and Diarrhoea

DR. MARTIN HOFFMAN, Montreal

Bronchoscopy in Lung Cancer, Its Practical Value in Detection and Management

DR. D. D. MUNRO, Montreal

SESSION B

2.00 p.m. - 4.30 p.m.

DR. CAMPBELL GARDNER, Montreal (*Chairman*)**The Management of Gastrointestinal Haemorrhage**

DR. R. G. CORKRAN, Quebec

The Management of Abdominal Emergencies in the Aged

DR. D. L. C. BINGHAM, Kingston

The Urological Complications of Trauma

DR. J. P. BRAULT, Montreal

Immediate or Operative Cholangiography and Manometric Pressure—100 Cases

DR. J. A. HECTOR BEAUDET, Quebec

SECTION OF RADIOLOGY

2.00 p.m. - 5.00 p.m.

DR. HENRI LA POINTE, Quebec (*Chairman*)**The Radiological Signs of Increase and Decrease in Intracranial Pressure**

DR. D. L. McRAE, Montreal

Follow-up Studies after Thorotrast Angiography

DR. ARNOLD BERRETT, Montreal

Unexpected Findings on Roentgen Examination of the Heart

DR. JULES LABERGE, Montreal

Eventration of the Diaphragm

DR. J. SCOTT DUNBAR, Montreal

Etude de l'Atelectasie dans la Coqueluche

DR. L. S. IVAN VALLEE, Montreal

Peritoneal Mice

DR. WOLFE LIGHT, Montreal

FOLKLORE PROGRAM FOR COUNCIL DINNER

The Council of the Canadian Medical Association will dine at the Château Frontenac on

Tuesday, June 12, with the Governor-General of Canada, the Right Honourable Vincent Massey, as guest of honour. The company will be entertained after dinner by Quebec groups of folk dancers and singers, "Les Villageois" and "Les



"Les Villageois."

Collégiens Troubadours". The program will include traditional and ritual dances, such as the old Canadian folk dances "Finding the Hare's Burrow", "The Repentant Shepherdess", "Ritual Dances of May" and various French Canadian square dances (Le Galop Double, Le Brandy Québécois). The Canadian folk song troupe "Les Collégiens Troubadours" will include in their recital the ever familiar song, "Alouette".

LADIES' PROGRAM

Madame Renaud Lemieux and her local committees have arranged an attractive program of entertainment for the wives of members attending the 89th Annual Meeting at Quebec. We reproduce herewith the events which will be of particular interest to the ladies. Please draw this announcement to the attention of your wife.

Monday, June 11

9.30 a.m. - 4.00 p.m.—REGISTRATION (Château Frontenac). Coffee will be served.

5.45 p.m.—Reception by His Excellency the Governor-General for members of General Council and their ladies and other invited guests (Citadel).

Tuesday, June 12

9.30 a.m. - 4.00 p.m.—REGISTRATION (Château Frontenac).

All-day tour. Buses will leave the Château Frontenac at 9.30 a.m. for the Shrine of Ste. Anne de Beaupré, then on to Manoir St-Castin for lunch and back to town for a sightseeing tour, returning to the hotel by 4.30 p.m. Price of tour including transportation, \$5.00.

7.00 p.m.—Annual Dinner to the General Council (Château Frontenac). All members and their wives are invited to purchase tickets for the dinner. His Excellency the Governor-General will be the guest of honour. Entertainment and dancing. **Formal dress.**

Wednesday, June 13

9.30 a.m. - 4.00 p.m.—REGISTRATION (Château Frontenac).

5.00 p.m.—Civic Reception (Château Frontenac) for all members and their wives.

8.00 p.m.—General Annual Meeting. President's Reception. Ball. (Château Frontenac).

Thursday, June 14

9.30 a.m. - 4.00 p.m.—REGISTRATION (Château Frontenac).

12.30 p.m.—Lunch for the ladies (Château Frontenac), with l'Abbé Maheux as guest speaker. Prize draws.

5.00 p.m.—Special Convocation at Laval University, to be followed by a "vin d'honneur" in the gardens of the Old Quebec Seminary if weather permits. All members and their wives are invited to attend.

Friday, June 15

10.00 a.m.—Farewell Coffee Party at the Archives Building on the Plains of Abraham. Host, Mr. Antoine Roy, Provincial Archivist.

MISCELLANY

OUR SOUTH AFRICAN "COLLEAGUES"

JOHN VALENTINE, M.B., Ch.B., L.M.C.C.,
London, Eng.

For the past few weeks I have been doing a locum in a predominantly native Bantu practice in South Africa. Here in Natal the people are mainly Zulus with a sprinkling of Basutos.

The witch doctors or "inyangas" have had the practice of medicine in their hands for hundreds of years and they are still a very active factor in the lives of the native people. Certainly their influence is felt every day in this practice.

The general charge for seeing a patient at the medical clinic is one dollar. For this they are examined by the European doctor and given the ordinary medicines. If they need penicillin they may be charged extra, while if the more expensive antibiotics are indicated they are sent to hospital where they receive them free. They do not get off so lightly with the inyanga. He requires them to pay \$1.50 just to see them. If he opens his bag in order to throw the bones, he charges extra. He will often make it a condition of treatment that, if the patient recovers, the family give him two goats or even an ox.

The following is a common technique at consultation. The inyanga and his patient sit in the middle of a circle of the patients' relatives and friends and the witch doctor tries to guess the patient's symptoms. The witch doctor's quality is estimated by the length of time he takes to locate the trouble. After each guess the crowd shouts out. The closer to the complaint, the louder the shouting; if he is off the track, the crowd grows quieter. Sooner or later he hits it. With this as a background it is easier to understand the patient who comes into the doctor's consultation room and when asked what is the matter will reply "I want you to tell me what is the matter." This is a common enough reply amongst Europeans, but the natives mean it and your reputation amongst them will depend upon your ability to locate their symptoms rapidly—a type of professional "Twenty Questions".

However, the native medical assistant will often come to your rescue and advise you to start off with "Have you bladder pains?" This is a safe bet because half the native population seems to suffer from this condition. The usual cause is said to be failure to drink enough water, but the high incidence of gonorrhoea and bilharzia may play a large part. If you miss on the first try, then there are clues to look for. When patients have a pain in any part of the body, they will scratch the skin and rub in irritating materials, which act as a counter-irritant to the original pain. If you see these abrasions, it is safe to ask whether the pain is in that area.

When one of the local women inyangas appeared at the clinic for examination I was lucky, for she had cystitis with painful micturition. The treatment with sulphonamides and alkalizing mixture was routine. But what to do about charging? We have been taught at medical school that we should not charge our professional colleagues. But again the native medical assistant came to my rescue: "We usually charge them the routine price, doctor."

The native people have great faith in an injection. They frequently ask for and are willing to pay for 2 c.c. of vitamin B complex, which seems to benefit them greatly. Their starchy diet is almost certainly badly lacking in the B vitamins, and heavy labourers claim especially good results from this injection. They say that they feel better before leaving the consultation room.

Each time the jeep pulls up at the weekly rural clinics a crowd of women are waiting with their young children who have been brought along for the free injection. Ten

c.c. of vitamin B complex is added to two litres of sterile water, and 1 c.c. of the mixture is given to anybody who asks. The medical assistant frequently has 20 babies yelling at the top of their voices before he calls you for the consultations. Some doctors use this faith in injections to give the triple vaccine supplied free by the South African government. The children can do with it: 30% of them die before maturity, mostly from gastroenteritis, pneumonia, whooping cough and diphtheria.

Many of the Europeans living here are of the opinion that the inyangas are becoming less numerous, but this is probably because there are not as many really famous practitioners as in the past. Certainly the native people circularized by a mission group are strongly of the opinion that not only are they more numerous but the schools for mystics are turning out more each year.

And the inyangas are responding to the challenge offered by modern medicine. Many carry stethoscopes they have not been trained to use, and antibiotics such as aureomycin stolen from wholesale druggists in Durban figure in their armamentaria. Many of their herbal remedies are effective. One of the drugs administered to counteract diarrhoea will frequently cause an ileus which has been known to go on to gangrene of a segment of bowel in children.

Their search for stronger medicine does not end with the antibiotics. The inyangas say that the strongest and most effective medicine for certain things is only to be made from parts of the human body taken from the victim while he or she is still alive. The victim may be old or young, mentally normal or an idiot. However it is very important that the parts of his body being taken for the "muti" are taken while he is still alive. Even in comparatively civilized parts of the country people still disappear, and when the police make enquiries nobody knows where they have gone. Two natives have appeared in court for selling relatives to inyangas. The first had sold his mentally defective son and the second had taken £40 for his mother who was almost 100 years old. The latter's son was 73 at the time, so he should have been old enough to know better. Ritual murder is also common enough in Basutoland for several European law officers to spend most of their time investigating cases. Here the rugged mountainous terrain makes the investigations difficult.

However even in the comparatively accessible and civilized parts of the country the inyanga problem is still of primary importance. Many missionaries who live closest to the native population consider that the inyangas are still the most powerful influence in Bantu society.

c/o New Zealand House,
The Strand,
London, W.C.2.

[In the foregoing, Dr. Valentine has not mentioned two hazards associated with consultation with witch doctors. Recently the *South African Medical Journal* (December 3, 1955) carried an account of an outbreak of tetanus which affected 10 persons out of 25 who had been treated by a witch doctor. The witch doctor had made multiple incisions into the skin and had rubbed in an ointment which was alleged to cure most ills, prolong life and increase virility. He succeeded in conveying tetanus to 10 out of his 25 clients, and two of these died in spite of early and efficient treatment by orthodox physicians. When he was apprehended, a tin of ointment was found in his possession and this contained a healthy culture of *Clostridium tetani*. The witch doctor had collected about £14 in fees as well as a goat and a mare. He was given a year's imprisonment. The second hazard is mentioned, although the case is not proven, in a subsequent issue of the *South African Medical Journal*. A doctor records that a number of patients have appeared at his office suffering from acute toxæmia after being given some drug by mouth by witch doctors. Unfortunately some legal complication prevented the Institute for Medical Research from analyzing the medication which had been administered.—Ed.]

ABSTRACTS from current literature

MEDICINE

Diagnostic Significance of Changes in Free, Esterified and Protein-Bound Cholesterol, Lipo- and Glycoproteins in Lymphoma and Multiple Myeloma.

S. I. MAGALINI, M. STEFANINI AND H. M. MARIN:
Am. J. M. Sc., 231: 155, 1956.

A simple technique has made possible the study of electrophoretic mobility of protein-bound cholesterol in normal individuals and patients with lymphoma and multiple myeloma. These studies have been extended to the analysis of the electrophoretic behaviour of the lipoproteins and glycoproteins in these diseases. In lymphoma, values for total cholesterol and cholesterol esters are strikingly and characteristically decreased in relapse and tend to revert to normal in remission. Protein-bound cholesterol is increased in the albumin and α -globulin fractions and decreased in β -globulin fractions in patients with active disease. Lipoproteins and glycoproteins follow a similar but less striking and predictable pattern. Alterations of free, esterified and protein-bound cholesterol are fairly typical of lymphoma and found almost exclusively in advanced stages of the disease. They are not due simply to abnormalities in the distribution of serum proteins, since they are not found in parenchymal liver disease, where serum protein changes are similar to those seen in lymphoma. In multiple myeloma, serum cholesterol level is normal and normally distributed among protein fractions; lipoproteins and glycoproteins are preferentially associated with the pathologically increased protein fractions. Similar alterations occur in liver disease. S. J. SHANE

Prevention of Experimental Tuberculosis with Isoniazid.

S. H. FEREBEE AND C. E. PALMER: *Am. Rev. Tuberc.*, 73: 1, 1956.

The demonstrated effectiveness of isoniazid in combating progressive tuberculosis has quite logically led to the idea that this antimicrobial agent might be effective as a prophylactic and that, if isoniazid were being taken at the time when a tuberculous infection occurred, it might prevent tuberculous disease from developing. If it could be proved that human beings were protected against tuberculosis while taking isoniazid, appropriate use of this drug might provide entirely new possibilities for the control, and perhaps even for the eradication, of human tuberculosis. With this in view, research workers in the U.S. Public Health Service have undertaken laboratory studies to determine the preventive effects of isoniazid on experimental tuberculosis in laboratory animals. This paper reports the first of these studies.

In this investigation, 1,224 young guinea pigs were randomly separated into a number of groups and subgroups. Some groups were given isoniazid and challenged with a large intraperitoneal inoculum of virulent tubercle bacilli, while other groups were held as various types of "controls". The isoniazid was administered in the drinking water in three different concentrations, so that some groups of animals received approximately 1 mg., others 5 mg., and the remainder 25 mg. of isoniazid per kg. of body weight per day.

Two main conclusions can be drawn from this study: (1) A daily dose of as much as 5 mg. per kg. of isoniazid, if started before the challenge infection and continued for only 10 weeks after such challenge, is apparently sufficient to prevent mortality from tuberculosis for at least 26 weeks, and to allow guinea pigs to grow in weight at the same rate as normal untreated, uninfected animals. (2) After an isoniazid-treated tuberculous infection, guinea pigs respond to a later, untreated tuberculous infection very much as they do after vaccination with B.C.G.

S. J. SHANE

Broncholithiasis.

L. K. GROVES AND D. B. EFFLER: *Am. Rev. Tuberc.*, 73: 19, 1956.

If lymph nodes adjacent to the tracheobronchial tree calcify, they become inert endogenous "foreign bodies" in an environment of constant motion, with a tendency to erode the wall of an adjacent bronchus and to enter the lumen, resulting in broncholithiasis. The present authors review experience with 27 cases of broncholithiasis seen between 1949 and 1954.

In this series, parenchymal calcifications invariably represent the end-stage of healing of granulomatous pulmonary disease, most commonly tuberculosis, histoplasmosis or other fungal diseases. The symptoms fell into three major categories: bleeding, cough, and bronchial obstruction with its usual results of emphysema, atelectasis, obstructive pneumonitis and bronchiectasis. Commonest presenting symptoms were fever, wheezing, dyspnoea and chest pain. In only a very few instances was broncholithiasis suggested as the etiological diagnosis, the complications being more frequently diagnosed. Treatment consisted of pulmonary resection, in various degrees, in most cases, with endoscopic removal of broncholiths in only a few.

The writers feel that an awareness of the possibility of the condition, with resultant increased diagnostic suspicion and increased use of the bronchoscope, should lead to more frequent and earlier diagnosis.

S. J. SHANE

SURGERY

Emergencies in General Practice. Assessment and Emergency Treatment of Burns.

A. B. WALLACE: *Brit. M. J.*, 2: 1136, 1955.

The treatment provided by the physician varies according to the severity of the burn. His attitude, however, towards any kind of burn is important. Not only can it influence the later course, but he can in this way encourage a more intelligent and practical approach to first aid in his area.

The reaction of the body to thermal trauma is clearly explained, followed by elaboration of the individual points in treatment. Details are given regarding the body's response to trauma, the shifts which take place in the distribution of body fluid, and renal damage, which may develop when a burn has been extensive and deep. The value of replacement fluids and requirement fluids is indicated.

The necessary steps in supportive therapy and the main phases in the healing process are outlined, and attention is drawn to two early complications of burns—pressure effects and oedema. The principles of early care are then summarized as follows:

Minor Cases Treated at Home.—(1) Cleanse and snip blisters; (2) apply absorptive dressings and keep dry (closed wound crust); (3) elevate affected part; (4) do not re-dress for 10 to 12 days; (5) if burn is on lower extremity, put patient to bed.

Cases Admitted to Hospital.—(1) Obtain brief history, and establish time of accident and therapy given; (2) estimate and chart extent and depth of burn; (3) weigh patient on admission to ward; (4) if burn is extensive, catheterize patient on admission; examine urine and chart hourly output; (5) administer fluid therapy without delay; (6) do no further damage to the surface; (7) avoid factors extending the lag period; (8) take colour photograph of burn in first 24 hours; (9) watch for pressure effects (obstruction of airway or of circulation to limbs); (10) establish and maintain a closed burn wound.

Prognosis varies. In general, superficial burns heal without scarring. With deep burns there may be both scarring and deformity. Early grafting diminishes such risk. Extensive burns, whether superficial or deep, may

lead to early death from oligæmic shock. In the author's opinion all burns of over 40% of the body surface, especially at the extremes of age, must be regarded as very dangerous to life.

MARGARET H. WILTON

OBSTETRICS AND GYNÆCOLOGY

Urinary Tract Injuries Resulting from Pelvic Surgery.

H. S. EVERETT AND R. F. MATTINGLY: *Am. J. Obst. & Gynec.*, 71: 502, 1956.

Urinary tract injuries, while one of the most serious hazards of pelvic surgery, need not occur frequently if careful attention is paid to the anatomy of the pelvic portions of the urinary tract. If such injuries are encountered, recognition and repair at the time of occurrence give a better prognosis than later recognition and repair. Serious injury to the ureter is best repaired by reanastomosis to the bladder, where the injury is low enough in the ureter to make this procedure possible.

In the case of ureteral ligation unrecognized at the time, immediate deligation is to be condemned, and temporary nephrostomy with later repair of the ureteral defect highly recommended.

Bladder injuries recognized and repaired at the time rarely, if ever, lead to any serious difficulty.

Vesico-vaginal fistulæ resulting from total hysterectomy can usually be successfully repaired on the first attempt by use of the Latzko technique of partial colpocleisis.

ROSS MITCHELL

Value of Culdoscopy in Gynecologic Diagnosis.

T. H. GREEN, JR.: *New England J. Med.*, 254: 214, 1956.

An analysis of 150 consecutive culdoscopies performed during a two-year period at the Vincent Memorial Hospital, Boston, is presented. Salient features of proper culdoscopic technique are briefly described, and the various indications for the procedure are discussed in detail.

Maximum effective utilization is aided if the procedure is kept as simple and readily available as possible and if a certain amount of imagination, seasoned by experience, is used in its application. Contraindications are seldom encountered; potential complications rarely occur, and with experience there should be very few failures or errors in diagnosis.

The wide variety of pathological conditions identified by culdoscopy in this group of patients is tabulated according to the indications for the examination, and illustrative case summaries are presented.

This experience has convincingly demonstrated the great value of this procedure in facilitating the diagnosis of a number of gynecological disorders. Culdoscopy frequently not only provides the clue to proper medical or surgical therapy but also makes it possible to avoid an otherwise necessary laparotomy.

ROSS MITCHELL

The Severity of Diabetes in Pregnancy.

W. S. JONES: *Am. J. Obst. & Gynec.*, 71: 318, 1956.

Two hundred and four viable pregnancies in diabetic women are reviewed in an effort to ascertain what, if any, correlation may exist between (a) the historical and vascular encroachments of the disease process; (b) the clinical severity as expressed by insulin requirement; and (c) the obstetrical complications and fetal loss. The information obtained suggests that: (1) The concept that age of onset, duration and evidence of vascular damage are criteria of severity in diabetes is a sound one. It should probably remain basic in any classification. (2) There is also a significantly higher incidence of the physiological complications peculiar to pregnancy, and of fetal loss, in those patients whose normal daily insulin requirement is high (50 units or

more). (3) Both these factors should be taken into consideration in the evaluation of the severity of a case of diabetes in pregnancy; and both should be included in the formation of a definitive classification of diabetes in pregnancy. (4) The White classification is a good prototype but there are practical objections to it in its present form. What is needed is a more simple and compact classification embodying the principles here outlined.

ROSS MITCHELL

UROLOGY

Trichomonas Vaginalis Infection in the Male.

W. E. COUTTS *et al.*: *Brit. M. J.*, 2: 885, 1955.

Trichomonas vaginalis infection of the male is becoming increasingly recognized. The parasite is described and its pathogenicity and mode of spread are discussed. Infection is usually by sexual contact, but contagion from fomites has been noted. Clinical and laboratory findings in both acute and chronic infection are described, and references are made to latent infection and the carrier state. The possible existence of a transient trichomonæmia is considered. Treatment of the acute stage is by urethral instillation of bactericidal drugs; chronic infection requires both general and local treatment. The medico-social aspects of trichomonal infection are discussed.

ROSS MITCHELL

RADIOLOGY

Evaluation of the Various Methods of Demonstrating a Hiatus Hernia.

J. W. BOYD *et al.*: *Am. J. Roentgenol.*, 75: 262, 1956.

This study was carried out in an effort to evaluate the importance of a variety of manœuvres in the diagnosis of hiatus hernia during radiological gastrointestinal examinations. A definite sequence of manœuvres was decided upon and carried out by all examiners. The patient was first observed fluoroscopically in the erect position while swallowing eight ounces of barium mixture, special attention being given to the gas bubble in the cardia. The table was then lowered to the horizontal and the Trendelenburg positions and the abdomen pressed upon by the examiner. Observation was continued during a Valsalva test and then during straight leg-raising. The patient was then rotated to the right lateral and prone positions.

In the course of 1,500 consecutive gastrointestinal examinations hiatus hernia was demonstrated in 2.3% of patients, whose average age was 60 years and two-thirds of whom were females. Of the 35 hernias demonstrated, only four required special procedures for their demonstration, the common advantage of these special procedures obviously arising from an increase in intra-abdominal pressure. The straight leg-raising manœuvre of the authors (having the patient raise both heels from the table) is a new method of raising the intra-abdominal pressure during the course of gastrointestinal examination.

NORMAN S. SKINNER

Radiation Hazard Evaluation and Control in Hospitals.

G. FERLAZZO *et al.*: *Radiology*, 65: 892, 1955.

The introduction of new radioactive materials, particularly isotopes, into hospitals has increased the exposure of personnel to radiation. On the other hand, there is so much discussion of atomic developments that many lay people have a false fear of possible radiation hazards. The authors discuss the problem in detail. They point out that the radiation physicist should exercise a constant watch on all sources of radiation within the hospital. All hospital personnel exposed to radiation should wear measuring devices, such as film badges,

and these should be checked regularly and accurate records kept of the resultant exposure of all such personnel.

With continual oversight of all sources of radiation by the hospital physicist, and with reasonable care on the part of exposed personnel, there is no real danger of harmful exposure. Radium and fluoroscopy still remain the most dangerous sources of radiation and require careful supervision. Radioactive isotopes do not present a serious hazard.

NORMAN S. SKINNER

Roentgenologic Study of a Human Population Exposed to High-Fluoride Domestic Water.

N. C. LEONE *et al.*: *Am. J. Roentgenol.*, 74: 874, 1955.

The public health measure of introducing fluorides into water supplies has given rise to controversy regarding possible deleterious effects upon humans ingesting the water. This mistaken belief arises from the reports of unusual changes described in cryolite and rock phosphate workers who absorb large quantities of fluorides. Many American communities have long used domestic water supplies containing natural fluoride concentrations ranging from one to six parts per million, and in a few communities the fluoride concentration in the water has been even higher. Rarely have roentgenologists observed or reported bone changes due to this fluoride ingestion.

The present report deals with the roentgenographic findings of a 10-year study of 237 persons, approximately half of whom lived in a high-fluoride area (Bartlett, Texas) where the water contains eight parts per million fluoride, while the other half resided in a control area (Cameron, Texas) where the water contained only 0.4 parts per million. These people were thoroughly studied roentgenographically in 1943 and again in 1953 under carefully controlled conditions of examination and with a remarkably complete follow-up of the original subjects.

This study demonstrates that excessive fluorides in a water supply may produce roentgenographic evidence of bone change (increased density or coarsened trabeculation) in approximately 10-15% of the exposed population. However, these changes are slight in degree and are not associated with other physical findings except for dental mottling in children who had lived in the high-fluoride area for the first eight years of life. There is suggestive evidence from this study that a high fluoride content of water may be beneficial in counteracting the osteoporotic changes of old age.

NORMAN S. SKINNER

Considerations of Ionizing Radiation in Childhood. Radiation Therapy in Pediatrics.

H. W. DARGEON AND R. F. PHILLIPS: *Am. J. Roentgenol.*, 74: 618, 621, 1955.

In the first article, the author discusses in a very general way the effect of ionizing radiations on children, both in diagnostic radiology and in radiotherapy. Several cases from the literature are quoted of children treated by radiotherapy for a variety of malignant conditions, some of these showing complications resulting from treatment. Although the author quotes dosages, he gives no time relationships to these dosages. Four of his own cases of malignant disease treated by radiotherapy are briefly quoted.

In the second article, the author points out that although cancer is the third commonest cause of death in children, it is nevertheless an uncommon disease; large series of cases are only obtained over a long period of time. The importance of the tumour-host relationship is suggested by several observations, notably the continued growth of a few hæmangiomas while the majority regress spontaneously, occasional spontaneous regression of metastases from neuroblastomas and Ewing's tumours, change of malignant neuroblastomas into benign ganglioneuromas, and unexpected regression

of some tumours after minimal treatment. The author feels that these observations underwrite the importance of treating malignant disease in childhood to try to postpone a fatal outcome and possibly allow a natural mechanism of tumour control to develop. The general assumption that normal tissues or malignant tumours are more radiosensitive in children than in adults is not necessarily true. In his experience the effects of radiation in children are identical with those in adults at the same dose levels and time intervals. Tumours which occur both in children and adults do not vary in their response to treatment in the two groups. The author warns against the indiscriminate use of radiation in non-malignant conditions in children, but feels that radiotherapy has an essential part to play in the management of childhood cancers.

In discussion of the latter paper Dr. Vincent P. Collins, of Houston, Texas, pointed out that a certain incidence of complications from radiotherapy is acceptable, just as an operative mortality for different surgical procedures is accepted.

JOHN A. CASKEY

Intravenous Cholecystocholangiography.

W. H. SHEHADI: *J. A. M. A.*, 159: 1350, 1955.

Intravenous Cholangiography in the Postcholecystectomy Syndrome.

J. McCLENAHAN, J. A. EVANS AND P. W. BRAUNSTEIN: *Ibid.*, p. 1353.

Oral Cholecystography with Iopanoic Acid (Telepaque).

L. REYNOLDS AND H. FULTON: *Ibid.*, p. 1358.

Experience with Five Orally Given Cholecystographic Mediums.

E. E. SEEDORF AND W. N. POWELL: *Ibid.*, p. 1361.

Visualization of the biliary tract in its intact state is a clinical investigative procedure which has advanced a long way since its inception by Graham and Cole in 1924. An excellent review of this advance was presented as a symposium before the section on radiology at the annual meeting of the American Medical Association and published in the above-listed articles.

At the present time there are three substances which give highly accurate radiological visualization of the gallbladder after ingestion. These substances, Priodax (iodaliphonic acid), Telepaque (iopanoic acid), and Teridax (iophenoxic acid), differ in chemical structure, are all well tolerated and all give cholecystograms of about the same diagnostic value. Telepaque perhaps gives the clearest gallbladder shadow and excels the other two media in the high percentage of cases in which it will outline the biliary ducts. It has the disadvantage of leaving radio-opaque residue in the gastrointestinal tract which rarely may somewhat obscure the gallbladder shadow.

It is important for the physician to realize that ingestion of any of the three described cholecystographic media may result in a false-positive test for albuminuria, and the results of urinalysis should be interpreted in the light of this possibility during the day or two following cholecystography.

Intravenous cholangiography with Cholografin is a recent and marked advance in this field. After intravenous injection of 40 c.c. of the medium there is excellent visualization of the biliary duct system in the majority of cases. For good results this procedure requires the supervision of the trained radiologist. It presents the first satisfactory method for clinical investigation of the biliary duct system after cholecystectomy and is also of value in the further investigation of a gallbladder which has not shown satisfactory filling after ingestion of one of the oral media. Intravenous cholangiography finds its greatest usefulness in the investigation of the patient who has continued or recurrent symptoms following cholecystectomy, the so-called post-cholecystectomy syndrome.

NORMAN S. SKINNER

THERAPEUTICS

Treatment of Pemphigus with Potassium Para-Aminobenzoate.

C. J. D. ZARAFONETIS, A. C. CURTIS AND J. M. SHAW: *Am. J. M. Sc.*, 231: 30, 1956.

Potassium para-aminobenzoate was administered in 18 to 24 g. total daily doses to 18 patients with various forms of pemphigus. All patients with pemphigus vulgaris who received KPAB therapy for more than a month responded with marked to complete suppression of the disorder. Pemphigus foliaceus responded incompletely, although 2 of 4 cases had good clinical improvement. In one patient a pemphigus erythematoses cleared completely, another had an intermediate response, and a third was only slightly improved. Definite benefit was experienced by the only patient of this group with ocular pemphigus. Results were gratifying in three patients treated with both KPAB and cortisone, after large doses of steroid therapy alone had failed to control their disease satisfactorily. The only potentially serious complication of KPAB therapy is hypoglycaemia. This may be avoided by interrupting therapy if the patient fails to eat for any reason at all. The drug may be resumed as soon as the patient is again eating normally.

It would appear that potassium para-aminobenzoate, properly administered, alone or in combination with steroid hormones, offers a valuable adjunct to the management of several forms of pemphigus.

S. J. SHANE

INDUSTRIAL MEDICINE

Patients with Healed Myocardial Infarction Should Work.

W. D. STROUD: *Geriatrics*, 10: 184, 1955.

That patients with healed myocardial infarction should return to work at some remunerative occupation is indicated in this article. Six case histories are presented, typical of patients who have returned to work and carried on successfully for a number of years. Patients, however, have been able to carry on only through the frequent use of nitroglycerin for retrosternal pain. Consideration is given to the role of physical effort, emotional stress and responsibility in the development of a coronary occlusion.

The author expresses opinions based on his own experience, and also those of several of his contemporaries and of other investigators in this field. There does not seem to be any proved explanation of the pathological processes involved in a coronary occlusion with myocardial infarction, nor has it been proved that an increase of steroids in the blood is a contributing factor. The caution necessary on the part of the physician when advising these patients is explained from the point of view of the patient and from that of the physician.

Although patients who return to work may at any time have another coronary occlusion, these occurrences are seldom directly attributable to their work. Patients with breathlessness on effort following coronary occlusion may continue in executive positions and sedentary occupations without noticeably increasing their amount of myocardial insufficiency.

Attention is drawn to the advisability of explaining carefully to each patient that, after recovery from an acute episode, the condition for which restrictions were ordered no longer exists. Reference is made also to the invalidism which often results from anxiety, and to the value of personality studies which enable the physician to understand the patient and to direct his progress.

MARGARET H. WILTON

OBITUARIES

DR. JOSEPH EUGENE NAPOLEON DE HAITRE, 79, a prominent Ottawa surgeon, died on April 5 after a brief illness. He was a native of Thurso, Que., and graduated from the University of Toronto. Later he studied in several European countries. During World War I he served as a captain in the Medical Corps in England and France, returning to Canada in 1920. For many years he was on the board of Ottawa General Hospital, from which he retired in 1942. Dr. De Haitre continued to practise until a few days before his death.

He is survived by two brothers and two sisters.

DR. ALEXANDER GIBSON, 73, internationally known orthopaedic surgeon, died suddenly in his office in Winnipeg on March 29.

Late in 1913 a young Scotsman came to Winnipeg to be Professor of Anatomy in Manitoba Medical College. Though he was quiet and unassuming it was soon evident that here was a man with rare gifts of learning and of teaching ability. A fellow graduate said of Gibson that he had one of the best brains that had come out of Edinburgh University. A year after his arrival the First World War broke out and he saw service in India and Egypt, including the torpedoing of his transport in the Adriatic.

On his return to Winnipeg he practised as an orthopaedic surgeon. For this he was well qualified: M.A. (Science) Edinburgh 1904, M.B., Ch.B. with first-class honours and Ettles scholarship 1908, service in Edinburgh Royal Infirmary, research work, postgraduate work in London crowned with F.R.C.S. (England) in 1913.

His profound knowledge of anatomy was directed by a mind singularly clear and logical. As Dr. Gordon Maclean said at the funeral, he could clothe the dry bones with living flesh. He devised the posterior approach in operations on the hip joint, and planned the operation in which a vitallium cup is fitted over the head of the diseased femur, an operation which brought relief to sufferers from arthritis.

Honours could not escape him. For his research work in anatomy he was made Fellow of the Royal Society of Edinburgh; in 1920 he became a Fellow of the American College of Surgeons; later he was made senior member of the American Orthopaedic Surgeons. He served as president of the Canadian Orthopaedic Association and of the Winnipeg Medico-Legal Society. He was a Life Member of the Winnipeg Medical Society and the Scientific Club of Winnipeg and Senior Member of the Canadian Medical Association.

His teaching and hospital appointments were: Professor of Anatomy, Lecturer in Applied Anatomy, Associate Professor of Surgery in charge of Orthopaedic Surgery, Orthopaedic Surgeon and Consultant to the Winnipeg General Hospital, and Director of Orthopaedic Surgery at Deer Lodge Military Hospital. Moreover, he found time in his later years to operate at Brandon Sanatorium and was happy when he could describe to the Winnipeg Medical Society a rare tuberculous bone lesion encountered there.

In the Second World War he was in charge of a Canadian Red Cross unit at Hairmyres, Lanarkshire, Scotland.

As a lecturer on scientific subjects he had few equals. Knowledge of the subject, logic and lucidity of thought and precision in expression combined to make even the abstruse seem simple. When the Royal College of Physicians and Surgeons of Canada met at Winnipeg in 1954, he delivered the Lecture in Surgery on The Vertebral Column. He published some 60 papers, mainly on anatomical and orthopaedic subjects.

He is survived by his wife, a sister and niece in Edinburgh and a nephew in Derby, England.

We mourn Alexander Gibson, scholar and gentleman.
R.M.

DR. JAMES CECIL HAY, 56, a former general practitioner in Port Angeles, died on March 19 at Ellensburg,

Washington. He was born in Victoria and graduated from McGill University in 1923. Dr. Hay practised in Port Angeles until 1951 and with the late Dr. W. M. Davidson established the Davidson and Hay Hospital and Clinic there in 1924. He was a fellow of the International College of Surgeons.

Dr. Hay is survived by his widow, two sons and a daughter.

DR. WILSON METCALFE JUDD, 36, a general practitioner in Havelock, Ont., died on April 10 at Kingston General Hospital. He was a native of Greermount, Que., and a graduate of McGill University. He set up practice in Havelock in 1948.

Dr. Judd is survived by his widow and four daughters.

DR. ARTHUR P. LECUYER, 84, a general practitioner in L'Acadie, Que., died last month at his home there. He was born at S.-Philippe de Laprairie and graduated from Laval University. He began general practice in L'Acadie in 1895.

Dr. Lecuyer is survived by his widow, three sons and four daughters.

DR. MAURICE E. LUNAU, 46, a general practitioner in Oakville, Ont., died on April 10 at Western Hospital, Toronto. He was born in Hamilton and graduated from the University of Toronto. Later he did postgraduate work overseas. Dr. Lunau began general practice in Oakville more than 20 years ago and was chief anaesthetist on the staff of Oakville-Trafalgar Memorial Hospital.

Dr. Lunau is survived by his widow, a son and daughter.

DR. OTTO NIEMEIER, a Hamilton surgeon and a member of the board of governors of Hamilton College, McMaster University, died on April 6 after a brief illness. He was born in Tavistock and graduated from the University of Toronto. Later he became a Fellow of the Royal Colleges of Surgeons of Edinburgh and of Canada. He had been chairman of the education committee of the Canadian Medical Association for ten years and was a former president of the Hamilton Academy of Medicine.

Dr. Niemeier is survived by his widow and two daughters.

DR. EDWIN B. ROACH, a former director of the Metropolitan Health Department of Burnaby, B.C., died suddenly on April 5 in Toronto. He was born in Nappan, Nova Scotia, and graduated from Dalhousie University. In 1911 he moved to Calgary. During World War I he served with the R.C.A.M.C. Dr. Roach was medical health officer of Burnaby from 1947 until 1951 and continued to work for the Metropolitan Health Board until two years ago.

He is survived by his widow, a daughter and two sons.

DR. WILLIAM G. SIDDALL, 65, an ear, nose and throat specialist at Alliance, Ohio, died last month at his home there after a six months' illness. Dr. Siddall was born in Lobo Township, Ont., and graduated from the University of Western Ontario in 1914.

He is survived by his widow, a son and two daughters.

DR. LEWIS THOMAS, a veteran medical practitioner of Halifax, died at the Victoria General Hospital on March 2 after a short illness. He was 82. Dr. Thomas was born in Stellarton, N.S., and was a graduate of the Dalhousie Medical School. After completing postgraduate work in London and Glasgow, he returned to practise in the city of Halifax. For more than 20 years he taught practical surgery at the Dalhousie Medical School. He is survived by his sister, Catherine, Mrs. A. T. Spark of Halifax, and a nephew, Dr. Lewis H. Thomas of Regina.

FORTHCOMING MEETINGS

CANADA

CANADIAN TUBERCULOSIS ASSOCIATION, 56th Annual Meeting, Sheraton-Brock Hotel, Niagara Falls, Ontario. (C.T.A., 265 Elgin Street, Ottawa, Ont.) May 15-19, 1956.

CANADIAN PUBLIC HEALTH ASSOCIATION, 44th Annual Meeting, Admiral Beatty Hotel, Saint John, New Brunswick. (Dr. G. W. O. Moss, Honorary Secretary, 150 College St., Toronto 5, Ont.) May 29-31, 1956.

CANADIAN SOCIETY OF PLASTIC SURGEONS, Annual Meeting, Chantecler Hotel, Ste. Adèle, Quebec. (Secretary-Treasurer, Dr. J. A. Drummond, 1414 Drummond Street, Montreal 25, Que.) June 1-2, 1956.

CANADIAN PÆDIATRIC SOCIETY, Delawana Inn, Honey Harbour, Ontario. (President, Dr. J. H. Ebbs, The Hospital for Sick Children, 555 University Avenue, Toronto 2, Ont.) June 4-6, 1956.

CANADIAN OTOLARYNGOLOGICAL SOCIETY, Château Frontenac, Quebec, Que. (Dr. G. Arnold Henry, Secretary, 328 Medical Arts Bldg., 170 St. George St., Toronto 5, Ont.) June 6-7, 1956.

CANADIAN OPHTHALMOLOGICAL SOCIETY, 19th Annual Meeting, Château Frontenac, Quebec, Que. (Dr. R. G. C. Kelly, 90 St. Clair Avenue West, Toronto 7, Ont.) June 7-9, 1956.

CANADIAN UROLOGICAL ASSOCIATION, 12th Annual Meeting, Alpine Inn, Ste. Adèle, Quebec. (Dr. D. Swartz, Secretary, C.U.A., 332 Medical Arts Building, Winnipeg 1, Man.) June 7-9, 1956.

SOCIETY OF OBSTETRICIANS AND GYNÆCOLOGISTS OF CANADA—1956 Annual Meeting, Manoir Richelieu, Murray Bay, Quebec. (Dr. F. P. McInnis, Secretary, Society of Obstetricians and Gynæcologists of Canada, 1230 Avenue Road, Toronto, Ont.) June 8-10, 1956.

CANADIAN MEDICAL ASSOCIATION, 89th Annual Meeting, Ecole de Commerce, Quebec, Que. (Dr. A. D. Kelly, General Secretary, Canadian Medical Association, 150 St. George Street, Toronto 5, Ont.) June 11-15, 1956.

CANADIAN RHEUMATISM ASSOCIATION, Annual Meeting, Room 312, Ecole de Commerce, Quebec, Que. (Dr. J. B. Frain, Secretary-Treasurer, Winnipeg Clinic Building, Winnipeg 1, Man.) June 14-15, 1956.

CANADIAN ANÆSTHETISTS' SOCIETY, Mont Tremblant Lodge, Mont Tremblant, Quebec. (Dr. R. A. Gordon, Secretary-Treasurer, C.A.S., 516 Medical Arts Building, 170 St. George St., Toronto 5, Ont.) June 18-20, 1956.

UNITED STATES

NATIONAL TUBERCULOSIS ASSOCIATION: AMERICAN TRUDEAU SOCIETY, Statler Hotel, New York, N.Y. (N.T.A., 1790 Broadway, New York 19, N.Y.) May 20-24, 1956.

CATHOLIC HOSPITAL ASSOCIATION OF THE U.S. AND CANADA, 41st Annual Convention, Milwaukee, Wisconsin. (C.H.A., 1438 South Grand Boulevard, St. Louis 4, Mo.) May 21-24, 1956.

FIRST INTERNATIONAL SYMPOSIUM ON VENEREAL DISEASES AND THE TREPONEMATOSES, Washington, D.C. (Dr. C. A. Smith, Division of Special Health Services, U.S. Public Health Service, Washington 25, D.C.) May 28-June 1, 1956.

THIRD NATIONAL CANCER CONFERENCE, Sheraton-Cadillac Hotel, Detroit, Michigan. (National Cancer Conferences Coordinator, American Cancer Society, 521 West 57 Street, New York 19, N.Y.) June 4-6, 1956.

AMERICAN COLLEGE OF CHEST PHYSICIANS, 22nd Annual Meeting, Hotel Sherman, Chicago, Illinois. (Executive Offices, A.C.C.P., 112 East Chestnut Street, Chicago 11, Ill.) June 6-10, 1956.

AMERICAN MEDICAL ASSOCIATION, Annual Meeting, Chicago, Illinois. (Dr. George F. Lull, 535 North Dearborn Street, Chicago 10, Ill.) June 11-15, 1956.

AMERICAN ELECTROENCEPHALOGRAPHIC SOCIETY, 10th Annual Meeting, Claridge Hotel, Atlantic City, New Jersey. (Dr. W. T. Liberson, Secretary, A.E.S., V.A. Hospital, Northampton, Mass.) June 15-17, 1956.

WORLD CONFEDERATION FOR PHYSICAL THERAPY, Second International Congress, New York, N.Y. (Canadian Physiotherapy Association, 8 Bedford Road, Toronto 5, Ont.) June 17-23, 1956.

SOCIETY OF NUCLEAR MEDICINE, Hotel Utah, Salt Lake City, Utah. (Secretary, Dr. R. G. Moffat, 2656 Heather Street, Vancouver 9, B.C., Canada.) June 21-23, 1956.

SIXTH INTERNATIONAL CONGRESS OF BLOOD TRANSFUSION, Boston, Massachusetts. (Professor I. S. Ravdin, President, New England Medical Center, Harrison Avenue, Boston 11, Mass.) August 29-September 2, 1956.

OTHER COUNTRIES

INTERNATIONAL MEDICO-ATHLETIC FEDERATION, 11th Congress, Buergenstock, Switzerland. (Dr. G. Schoenholzer, Secretary-General, Bluemlisalpstr. 7, Muri-Berne, Switzerland.) May 29-June 1, 1956.

THIRD INTERNATIONAL SCIENTIFIC CONFERENCE ON RHEUMATISM, Aix-les-Bains, France. (M. Graber-Duvernay, 6 rue de Liège, Aix-les-Bains.) June 28-July 1, 1956.

BRITISH MEDICAL ASSOCIATION, Annual Meeting, Brighton, England. (The Secretary, B.M.A. House, Tavistock Square, London, W.C. 1, England.) July 5-13, 1956.

FIFTH INTERNATIONAL CONGRESS ON GASTROENTEROLOGY, London, England. (Mr. Hermon Taylor, 14 Upper Harley Street, London W.1.) July 18-21, 1956.

INTERNATIONAL SYMPOSIUM ON MEDICAL-SOCIAL ASPECTS OF SENILE NERVOUS DISEASES, Venice, Italy. (Secretariat, International Association of Gerontology, Viale Morgagni 85, Florence, Italy.) July 20-21, 1956.

SIXTH INTERNATIONAL PÆDIATRIC CONGRESS, Copenhagen, Denmark. (Dr. J. Vesterdal, Domus Medica, Kristianiagade, Copenhagen.) July 22-27, 1956.

EIGHTH INTERNATIONAL CONGRESS OF RADIOLOGY, Mexico City, Mexico. (Secretariat, I.C.R., Calle del Oro, 15, Mexico, D.F.) July 22-28, 1956.

20TH INTERNATIONAL PHYSIOLOGY CONGRESS, Brussels, Belgium. (Professor J. Reuse, Faculté de Médecine et de Pharmacie, 115 Boulevard de Waterloo, Brussels.) July 30-August 5, 1956.

FIRST INTERNATIONAL CONGRESS OF HUMAN GENETICS, Copenhagen, Denmark. (The University Institute for Human Genetics, Tagensvej 14, Copenhagen.) August 1-6, 1956.

EIGHTH INTERNATIONAL CONFERENCE OF SOCIAL WORK, Munich, West Germany. (J. R. Hoffer, 345 East 46 Street, New York 17, N.Y.) August 5-10, 1956.

WORLD FEDERATION FOR MENTAL HEALTH, Ninth Annual Meeting, Berlin, West Germany. (The Secretary, W.F.M.H., 19 Manchester Street, London, W. 1, England.) August 12-18, 1956.

FOURTH INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST, Cologne, West Germany. (Dr. Murray Kornfeld, American College of Chest Physicians, 112 Chestnut Street, Chicago 11, Ill.) August 19-23, 1956.

SECOND INTERNATIONAL CONGRESS OF PHYSICAL MEDICINE, Copenhagen, Denmark. Dr. B. Strandberg, Koebenhavns Amts Sygehus i Gentofte, Hellerup, Denmark.) August 20-24, 1956.

PROVINCIAL NEWS

ALBERTA

Dr. L. O. Bradley, who has been administrator at the Calgary General Hospital for the past 3½ years, is leaving on September 1 to take over a similar position at the Winnipeg General Hospital. While in Calgary, Dr. Bradley was responsible for the development of the five-step master plan governing the expansion of the General Hospital. This program is well advanced and it is expected that all but the final phase, the building of a Chronic Wing, will be completed before the end of 1957.

Dr. Bradley holds numerous executive positions in national and international hospital bodies and takes with him to Winnipeg a fine record of service in Alberta.

The Medical Executive of the Alumni Association of the University of Alberta recently voted to set up a loan fund to assist doctors to take a second year of internship. Assistance will be given at the rate of fifty dollars a month, with possibly more under exceptional circumstances.

Repayments are to be made on a specified basis, starting one year after the completion of the second year of internship.

W. B. PARSONS

SASKATCHEWAN

A new 25-bed psychiatric wing is to be opened at the Moose Jaw General Hospital this year, and psychiatric services at the University Hospital, Saskatoon, are to be extended at a total cost of \$21,000.

The Moose Jaw psychiatric wing is planned to provide services similar to those given in the Munroe Wing at the Regina General Hospital.

During April the Uranium City Hospital and staff residence were officially opened by the Honourable T. J. Bentley, Minister of Public Health, according to a Bureau of Publications release. This single-storey hospital can accommodate 25 patients, and has excellent provision for surgical and obstetrical services, as well as x-ray, clinical, laboratory and public health facilities. The new hospital will serve the entire population of the Beaver Lodge local development area, currently estimated at 4,000, and its accommodation consists of 11 medical and surgical wards, two private isolation wards, 3 children's wards, 9 maternity wards and a nursery with 14 bassinets.

The total cost of construction for the hospital and staff residence was approximately \$100,000, toward which the Provincial and Federal Governments made grants totalling \$90,000.

At the recent annual meeting of the Saskatchewan Branch of the Canadian Public Health Association held in Regina, delegates passed a resolution authorizing the executive to make an award to the hospital which, considering its resources, made the greatest contribution towards stimulating concord between curative and preventive medicine.

The Association also resolved to request that the proposed Federal-Provincial Hospital Insurance Plan should include provision for hospitalization of the mentally ill and tuberculosis patients.

The Provincial Government is to be asked to proceed with the plan to provide full-time public health services for the entire province by encouraging the establishment of health regions in areas not yet organized. The delegates passed a resolution that these public health services should have priority over all other health services, and that public education and organization for this purpose should be instituted in advance.

In view of the need to integrate medical, nursing and administrative techniques, a recommendation will be made to the provincial government that in the future the chronically ill be accommodated in additional divisions or departments at general hospitals rather than in independent isolated institutions.

The Association also passed a resolution to impress upon schools of public health and other training establishments the importance of widening the preparation of health workers for leadership demands of a comprehensive modern public health program.

At the last regular monthly dinner meeting of the Regina and District Medical Society held in conjunction with the postgraduate course in obstetrics and paediatrics on Friday, April 6 at the Hotel Saskatchewan, Dr. J. L. McKelvey, Professor and Head of the Department of Obstetrics and Gynecology at the University of Minnesota, addressed the members present on "The Present Status of Gynaecological Malignant Diseases".

A Federal-Provincial diagnostic grant of \$12,000 has been received by the Kamsack Union Hospital towards the cost of new x-ray equipment. Rated at 500 milliamperes, it replaced one of 100 milliamperes capacity which was installed in 1950.

A proposal to build a \$3,000,000 addition to St. Paul's Hospital, Saskatoon, has reached a stalemate because the Department of Public Health refused to recognize the need for, and authorize an increase in the bed capacity of the institution. This was stated at a meeting of St. Paul's Hospital Board called to devise means to overcome the situation.

The proposed extension had been agreed on following a recommendation of the Medical Advisory Board that in order to meet the health needs of the community, and of Saskatoon as a growing medical teaching centre, the bed capacity of the hospital be increased to 376. There was also a need for departmentalization among the various wards in the hospital. The Hospital Board decided to reiterate this recommendation of the medical group to the Department of Public Health through the Honourable T. J. Bentley, Minister of Public Health, in the hope of getting official recognition of the plan. In addition, the Chairman of the Board, E. M. Hall, Q.C., was authorized to appoint a committee of three to work in arousing public interest in the proposal.

In outlining the previous developments, Mr. Hall said that a new wing for St. Paul's Hospital had been contemplated for two years to provide the modern services necessary and allow for the departmentalization recommended. An architect had drawn up plans for a wing on the north side. Negotiations had been opened with the Department of Public Health and Mr. Bentley, in which the size of the hospital, proved bed capacity, and costs involved were dealt with.

G. W. PEACOCK

MANITOBA

Dr. Gordon MacKenzie of Strathclair travelled by a team and sleigh to a farm in the district, gave first aid and transported to town Gordon Mackie, aged 22. The young man had his left leg amputated below the knee by the blower on a tractor-mounted snow plow while he was clearing a road on his snow-bound farm. Mr. Mackie was transported from Strathclair to Brandon hospital on a stretcher rack on the outside of a Sikorsky helicopter, piloted by an army pilot from Rivers; he is reported to be in good condition.

The Manitoba Clinic held open house in its new building at Sherbrook and McDermot, Winnipeg, on the afternoon of March 30. The building adjoins the Winni-

peg General Hospital, the new Children's Hospital and the Medical College.

The Manitoba Red Cross transported food to Duck Bay from Winnipegosis. The town's general store containing its food supply was destroyed by fire on March 26 and earlier attempts to bring in food failed because of snow-blocked roads.

Great Northern Railway surgeons will meet at the Fort Garry Hotel, Winnipeg, May 28 and 29.

Professor Colin Ferguson and Dr. Bruce Chown have been appointed to the National Advisory Committee of the Canadian Red Cross Society.

At the annual meeting of the North of 53 Medical Association, Dr. Stuart L. Carey, Medical Superintendent of Clearwater Lake Sanatorium, was elected president for the current year. ROSS MITCHELL

ONTARIO

The London Academy of Medicine held its annual Academy Day on April 18. Dr. K. MacFarlane, McGill University, and Dr. Joseph Janes, Mayo Clinic, were the guest speakers. Dr. Janes spoke on "Emergency Treatment of Acute Injuries to the Extremities" and conducted an orthopaedic clinic. Dr. MacFarlane spoke on "Ectopic Pregnancy" and held a gynaecological clinic. A dinner and dance was held at the Hotel London.

Dr. Robert T. Noble, 85 years old, who recently retired as registrar of the College of Physicians of Ontario, was the guest of honour at a College Council dinner given at the York Club, Toronto. Twenty of his colleagues, including a son and grandson, heard him praise the general practitioner as "the flower of the medical profession".

Dr. C. H. Best has been elected a member of the Royal Danish Academy of Sciences and Letters.

The second residential home for elderly diabetics in England is to be opened at Parkgate, near Chester, in July. It will be called "The Charles H. Best Home". The first one, opened in 1953, at Kingston Hill, Surrey, was called the "Frederick Banting House".

The annual Sunnybrook Hospital staff dinner was held at the R.C.A.F. station. Guests of honour were Dr. R. I. Harris, Department of Surgery, and Dr. A. C. Norwich, formerly district medical officer and superintendent of the Red Chevron Veterans Home, who have recently retired. Dr. J. N. Crawford, Director General of Treatment Services, was present. General W. H. S. Macklin, recently retired Adjutant-General, spoke on "Problems in Canadian Defence".

The Public Health Act regarding prenatal examinations was passed in October 1946, as a measure towards reduction of the incidence of congenital syphilis. The aim has been realized to such an extent that recognition is now being given to other more pressing problems in prenatal work. The present fee paid for prenatal examinations is being discontinued. A free laboratory Rh typing service to physicians and assistance to general hospitals for the improvement of newborn nursery facilities is now in effect.

Dr. Sidney Weinhouse, Institute for Cancer Research and the Lankenau Hospital Research Institute, Philadelphia, gave three lectures in the Department of Physiology, Toronto. They were: "Alternate Pathways of Glucose Metabolism in Normal and Neoplastic Cells", "The Intermediary Metabolism of Cancer Cells" and "Certain Aspects of the Biosynthesis of Amino Acids".

Dr. A. L. Chute, Professor of Paediatrics, University of Toronto, addressed the Essex County Medical Society on "Abdominal Pains in Childhood". He mentioned physiological causes, hunger and colic; pathological causes such as infection, mechanical and general systemic disease as blood dyscrasias, vascular disease including emboli or thrombosis; collagen disease such as periarteritis or lupus; allergies; colitis as found in Crohn's disease; neurological conditions; osseous, muscular or cutaneous causes, and finally psychological causes.

The approach to the problem is via a complete history and physical examination; removal of infected foci; low-fat, milk-free diet; upper and lower gastrointestinal studies; pyelograms and cystograms; gallbladder x-rays; spine x-ray if tuberculin test is positive; laparotomy for Meckel's diverticulum or appendicitis.

LILLIAN A. CHASE

The Toronto Academy of Medicine held its annual Library and Historical Night on Tuesday, April 10. The evening began with a dinner at the Granite Club, in which about 100 persons participated. The company then moved down to the Academy to hear a lecture by Professor Joslyn Rogers, the well-known analytical chemist and forensic expert. Before Dr. Rogers's lecture, an Honorary Fellowship was conferred on Dr. T. C. Routley, President of the British and Canadian Medical Associations. This distinction is comparatively rarely awarded by the Academy and is therefore all the more prized. Dr. Routley was introduced by Dr. Ian Macdonald and the Honorary Fellowship was conferred by the President of the Academy, Dr. P. A. Sarjeant. Dr. Rogers talked for over an hour on various aspects of forensic chemical work, drawing upon the rich experiences of a long and varied life in the service of justice. He produced from his brief-case many exhibits, with the dexterity and aplomb of a professional conjurer. He told his audience various details of safe-cracking and fire-setting, and discoursed on a number of poisoning cases which he had encountered. His audience was obviously spellbound by these reminiscences. The meeting then dispersed throughout the Academy to view the hobby show. The greater part of the show was composed of paintings in oils and watercolours done by members of the Academy, together with an exhibit of paintings owned by members and including some examples of the work of the Group of Seven. Among other exhibits were a number of handpainted ties, a dinner wagon and colour photograph transparencies. An enjoyable evening came to an end after the serving of light refreshments.

NOVA SCOTIA

Dalhousie University Medical School has been pleased to announce the appointment of Dr. C. E. Marshall of Australia to the post of Associate Professor of Pathology.

Dr. J. Ray MacLean of Halifax was elected Chairman, and Dr. Donald I. Rice, Secretary, of the Halifax-Dartmouth Branch of the College of General Practice.

A National Cancer Institute grant in the name of Dr. G. W. Bethune of the surgical staff of the Victoria General Hospital has been announced. The grant will enable new research on special procedure at the Nova Scotia Tumour Clinic at the Victoria General Hospital. This grant is especially designed for treatment of patients with far-advanced cancer, and will provide for three years' further research. It is hoped at the end of this time that further funds will be made available for this important undertaking.

Dr. Norman G. B. McLetchie has tendered his resignation as Professor of Pathology at Dalhousie Medical School. This resignation will be effective on August 31, 1956. Dr. McLetchie has held the post of Professor of Pathology and Provincial Pathologist for the past six years.

Dr. J. S. Robertson, Deputy Minister of Health, has announced that his Department has sufficient poliomyelitis vaccine to vaccinate 87,696 children in 1956. It was hoped to commence this vaccination on or about the 15th day of April.

The Post-Graduate Committee of the Faculty of Medicine at Dalhousie University in co-operation with the Department of Surgery presented a week in surgery, April 23 to 27, 1956. The guest lecturer was Dr. M. M. Hoffman, Associate Professor of Medicine, McGill University, and Physician in Chief, Jewish General Hospital, Montreal.

WALTER K. HOUSE

BOOK REVIEWS

TEXTBOOK OF NEUROLOGY. H. H. Merritt, Professor of Neurology, Columbia University, New York. 746 pp. Illust. Lea & Febiger, Philadelphia; The Macmillan Company of Canada Limited, Toronto, 1955. \$12.50.

This new textbook of neurology is essentially a practical guide for clinicians, and is written for senior students and general physicians. It is assumed that readers are already acquainted with the anatomy and physiology of the nervous system as well as the methods of examination.

The descriptions of clinical syndromes, grouped where possible in relation to etiology, are concise and clear, and the allotment of space in accordance with the importance of the disease is very satisfactory. Enough pathology and laboratory work is given for an understanding of clinical features, and the sections on treatment are adequate and realistic. Tables showing, for example, frequencies of involvement of certain structures in diseases, or relative different types of tumour, are a helpful feature of this text. Illustrations are good, and there is an adequate bibliography for further reading.

ATLAS OF RUSH PIN TECHNICS. L. V. Rush, Department of Surgery, Rush Memorial Hospital, Meridian, Mississippi. 277 pp. Illust. The Berivon Company, Meridian, 1955.

This atlas is divided into three sections. The first deals with dynamics, stability of fixation, general considerations of bone healing, delayed healing and non-union. The second and third sections deal with specific techniques for fractures of the lower extremity and upper extremity respectively.

The illustrations, which are profuse, are extremely clear. Each condition is described, for the most part, on one page or else two facing pages. This facilitates reading. The short descriptions are quite clear.

This book is designed for the experienced surgeon, to present a specialized concept for the treatment of extremity fractures. It would be certainly useful to someone contemplating the use of Rush pins, and so might well be kept in medical reference libraries. It is doubtful if any surgeon would wish to have it in his personal library.

VASCULAR SURGERY IN WORLD WAR II. D. C. Elkin, Professor of Surgery, Emory University, Georgia; and M. E. DeBakey, Professor of Surgery, Baylor University College of Medicine, Houston, Texas. 495 pp. Illust. Office of the Surgeon General, Department of the Army, Washington, D.C., 1955. \$4.25.

This survey of the conduct of vascular surgery in the U.S. Forces during World War II contains valuable details on the clinical and laboratory investigation of traumatic and non-traumatic vascular lesions. The care of these lesions is portrayed from field care to vascular centre, interior zone. Various arterial repair and grafting techniques, with the results, are given in detail. Similarly, aneurysms and arteriovenous fistulae are thoroughly dealt with, many case reports detailing the management of fistulae in various locations in limbs, body and head. Sympathectomy in relation to the above lesions, arteriosclerosis, Buerger's disease and Raynaud's phenomenon is discussed fully. References, illustrations and diagrams are excellent throughout.

THE MECHANISMS OF HEALING IN HUMAN WOUNDS. S. W. Hartwell, Chief of the Surgical Service, Mercy Hospital, Muskegon, Michigan. 166 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1955. \$5.25.

This illustrated monograph forms one of the American Lecture Series. Healing of the various tissues in the human is described as seen by the author. It would seem to the reviewer that many words are taken to state the obvious and known. Some of the statements one cannot agree with: for example, "this fact . . . explains the feasibility of burying dermic grafts." Or again, "It is not generally appreciated that the primary result of a surgical incision in any tissue is inflammation."

Nevertheless this small volume presents much earnest work done by one interested in the problem of wound healing and its perusal will prove both interesting and provocative.

CORNEAL GRAFTS. B. W. Rycroft, The Corneo-Plastic Unit and Eye Bank, Queen Victoria Hospital, East Grinstead, Sussex, England. 286 pp. Illust. Butterworth and Co. Ltd., London, 1955. \$11.50.

The subject of corneal grafts is discussed by leading workers in the field. A book written by many authors frequently is disjointed, being irregular both in the sequence of topics and in the quality of the sections. This book suffers little from such defects; the chapters follow each other in natural sequence, and each author's contribution is of good quality.

Several of the chapters are particularly worthy of mention. Hugh Dawson writes of the anatomy and the physiology of the cornea, discussing the construction which permits the cornea to be clear and the metabolism which is necessary for clarity to be maintained. Pathological considerations of corneal transplantation are described by Guy Offret. The operative techniques and general care of full thickness grafts are discussed by Barraquer Moner, and of lamellar grafts by Paufigue. The chapter by Castroviejo is devoted to keratectomies and retransplants. Tudor Thomas very ably discusses the complications of keratoplasty. There is an excellent chapter on the preservation of the donor material by Billingham and Rycroft. Maumenee presents a fundamental concept of the biological problem of the acceptance of donor material by the host. One of the most interesting chapters is that by Rycroft, describing the many special instruments used in keratoplasty.

References are given at the end of each chapter, but of particular value is a 28-page bibliography at the end of the book. This alone makes the book a useful guide for workers in the field.

The book is clearly printed, on good paper, with clear and well-chosen illustrations. It is of convenient size and is firmly bound. The index is adequate.

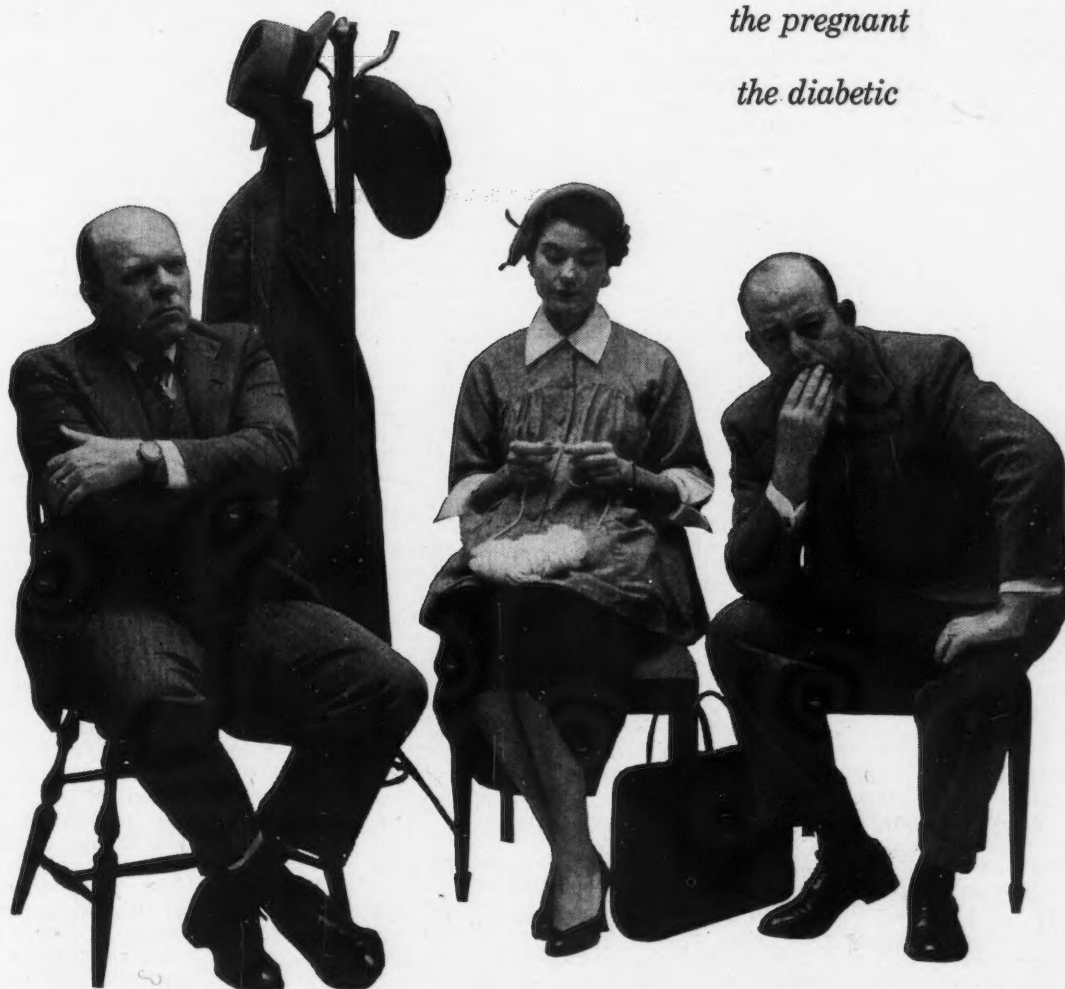
(Continued on page 858)

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LE MECANISME PHYSIO-PATHOLOGIQUE DE L'ECZEMA (The Physio-pathological Mechanism of Eczema). Edited by J. Charpy, Professor, The Dermato-Syphilological Clinic of the Faculty of Medicine, Marseilles. 288 pp. Illust. Masson et Cie., Paris, 6e, 1954. 1,600 Fr. fr.

This book is a collection of the papers given at a three-day meeting of the Marseilles section of "La Société Française de dermatologie et de syphiligraphie" in October 1953. It consists of 15 main reports, 7 of which were given by Charpy and/or his associates. There are abstracts of the discussion of the main reports and also some 20 short communications.

The principal features of the work are chapter II, on the histopathology of eczema, and chapter VI, on the role of the nervous system in eczema. There are also chapters on patch tests, their techniques and interpretations; on the immunological aspects of eczematous sensitization; and on the role of micro-organisms in the pathogenesis of eczema.

The histopathology of the early stages of eczematous contact-type dermatitis is demonstrated by photographs of skin biopsies, taken at varying intervals between one hour and 48 hours, at the sites of patch tests with chemicals on sensitive human subjects. The photographs are so arranged as to show the chronological development of the lesions.

Charpy presents his conception of the role of the nervous system in eczema. According to him, the mechanism of eczema is not explained adequately by the classical immunological concepts. He offers a neuro-vegetative theory. He reports the results of his experiments on the nervous system of guinea pigs, in which eczematous sensitization was produced. He concludes that eczema is due to a reaction of the central nervous system. Some of his explanations, even though they are appealing, might not be entirely acceptable. This is a very controversial theory.

LA LEPRE (Leprosy). R. Chaussinand, Head of the Leprosy Department, Institut Pasteur, Paris. 312 pp. Illust. 2nd ed. Expansion Scientifique Française, Paris, 1955. 3,500 Fr. fr.

This monograph on leprosy is written by an acknowledged expert on the subject. Dr. Chaussinand is the Chief of the Leprosy Service of the Pasteur Institute, Paris, and has been on the panel of experts of the World Health Organization for some time. The present edition of his book has been considerably modified from the first which appeared in 1955. Dr. Chaussinand discusses in great detail the classification of leprosy, describing the classifications suggested by the WHO Expert Committee and the Sixth International Congress of Leprology. He offers a classification differing slightly from both of these, but giving considerably greater detail. He has introduced new material into this edition on the prophylaxis of leprosy and also on treatment, which he dis-

cusses at great length. He closes the book by saying that 20 years ago the active treatment of leprosy was almost negligible. Now the situation has changed and there are effective methods of prophylaxis and therapy available. However, out of the 5 million human beings suffering from leprosy, scarcely 400,000 are receiving regular treatment. An immense task remains to be accomplished.

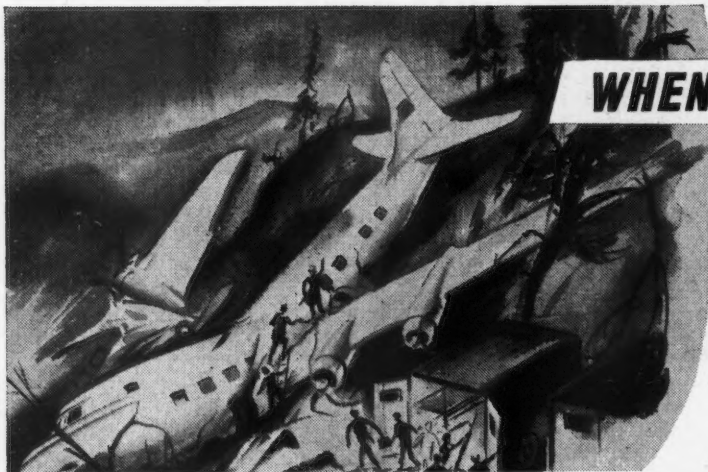
BIOLOGIE DES MALADIES DUES AUX ANAEROBIES (Biology of Anaerobic Infections). A. R. Prévot, Institut Pasteur, Paris. 572 pp. Editions Médicales Flammarion, Paris, 1955. 2,225 Fr. fr.

Dr. Prévot, who is at the Pasteur Institute, Paris, in 1937 summed up the literature on anaerobes and their diseases. In the present volume he brings the story up to date by summarizing research which has taken place in the period 1937 to 1955. For prior work the reader is referred to his previous book, except in the case of conditions whose significance has only aroused interest since then. The book is not clinically oriented; the author gives sufficient clinical data to act as a skeleton for his story, but most of the material is strictly bacteriological. Thus the volume is in the main an analysis of bacteriological, biochemical, immunological, serological and therapeutic studies which have been pursued throughout the world since 1937. An enormous amount of reading has gone into the production of this book; in his preface the author mentions 2,300 publications of this period. He has introduced as little personal comment or criticism as possible, but summarizes conclusions at the end of each chapter. There is an extensive bibliography at the end of each chapter.

HEMATOLOGY. C. C. Sturgis, Professor of Internal Medicine, University of Michigan Medical School. 1,222 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1955. \$21.50.

When the first edition of this book appeared in 1948, it was favourably received. The second edition has been very extensively revised; such important advances in hæmatology as the isolation and identification of vitamin B₁₂, the therapeutic uses of ACTH and cortisone in hæmatology and the development of such drugs as the folic acid antagonists are described in considerable detail. Though this monograph exceeds 1,100 pages, it is a very readable book. The historical approach to the different conditions is stressed and given more space than is usual. In his preface to the first edition, Dr. Sturgis suggested that the ideal situation in hæmatology was for its practice as a specialty by a physician with a good background and training in internal medicine. This book reflects such a standpoint; due emphasis is given to the clinical rather than the laboratory aspects of the subject, although laboratory tests are adequately described.

(Continued on page 860)



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THE DIAGNOSIS AND MANAGEMENT OF UROLOGICAL CASES. B. W. T. Pender, Senior Surgical Registrar, St. George's Hospital, London, and J. O. Robinson, Senior Surgical Registrar, St. Bartholomew's Hospital, London. 170 pp. Illust. Baillière, Tindall and Cox, London; The Macmillan Company of Canada Ltd., Toronto, 1955. \$3.60.

This book was designed to serve as an introductory guide to urology, for use by students, residents and general practitioners. The authors have intentionally omitted extensive discussions of pathology and methods of therapy. Adequate coverage is given to the most common urological conditions, while the less common disease processes are very briefly considered. Following the presentation of the fundamentals of the urological history, examination, and special investigations, the disease processes affecting the various parts of the genitourinary system are discussed. A special chapter on genitourinary tuberculosis is included, as well as an appendix in which drugs and procedures used in urology are outlined.

A chapter on the adrenal gland is not included. Also omitted are some of the newer diagnostic tests, e.g., aortography, perirenal air insufflation, and needle biopsy of the prostate. Several statements were found whose accuracy could be challenged. For example, the authors state that the prognosis for teratoma and seminoma of the testicle is about equal. This is contrary to the generally accepted figures. They also suggest that a biopsy be taken by the transurethral route in suspected cases of carcinoma of the prostate. This route is considered inadequate in all but the late malignancies of the gland.

The urological beginner will likely find the book of benefit chiefly because of its brevity. In it he will find guidance for many of the problems encountered in the outpatient department and on the ward. The authors have accomplished their aim by presenting a handbook to serve as an introduction to urology.

SELF-HELP FOR THE ARTHRITIC. David White, Senior Physiotherapist, the Walnut Tree Hospital, Sudbury, England. 55 pp. Illust. Henry Kimpton, London, 1955. \$.75.

This little hand-book is written for patients, and rightfully emphasizes the vital part the patients themselves must play in the prevention of deformities by regular daily exercise and rest. The author mentions the many advances in the rheumatic field with new drugs and methods, but fortunately stresses the fact that these are only part of the treatment and rest and exercise remain essential parts of the program. No efforts on the part of the doctor or physiotherapist will be successful without the co-operation of the patient.

Correct diagnosis is essential, as there are many different forms of arthritis requiring different treatments. The author is perhaps a little over-optimistic when he suggests that the preservation of joint movement, the avoidance of deformities and progression of the disease can be achieved by proper exercise, rest and the avoidance of stresses of all kinds, particularly worry and mental stress. However, he rightfully recognizes the tremendous value of dogged determination and good morale in getting results.

Exercises for the various joints are described with excellent drawings. This is a good handbook for the arthritic patient.

COUNSELING IN MEDICAL GENETICS. S. C. Reed, Director, Dight Institute for Human Genetics, The University of Minnesota, Minneapolis. 268 pp. W. B. Saunders Company, Philadelphia, 1955. \$4.00.

Dr. Sheldon Reed, who is director of the Dight Institute for Human Genetics at the University of Minnesota, has prepared a small book giving a succinct discussion of the new field of genetic counselling. Dr. Reed points out

that a patient expects to receive from his family doctor genetic counselling of the same high quality as the surgical or medical counselling. Yet most physicians have little or no training in medical genetics. This small book is intended to aid such counselling at the "grass-roots" level; from there the physician may direct the patient on to advice from the professional geneticist.

In 29 short chapters, problems most frequently met with are briefly discussed, such as cousin-marriages, mongolism, club-foot, hare-lip and cleft palate, mental retardation, pyloric stenosis, disputed paternity, and diabetes.

Some might criticize the book as being inadequate, but from a number of physicians we have heard much praise. To them the presentation is straight to the point and fairly light and easy reading. The book reflects the kindly, friendly personality of the author and serves as a stimulating, though at times provocative, introduction to the field of counselling in medical genetics.

It is recommended as a useful book for physicians and surgeons.

MODERN METHODS OF FEEDING IN INFANCY AND CHILDHOOD. D. Paterson, Consulting Physician to Westminster Hospital, London, and G. H. Newns, Physician to the Hospital for Sick Children, Great Ormond St., London. 188 pp. Illust. Constable & Company, Limited, London, 1955. 15/-.

This book is a general outline of the normal care and feeding of the infant and small child and includes sections on breast feeding, artificial feedings, diets of older children, diarrhoea, vomiting, colic, constipation, the underdeveloped infant, and diets for sick children. In general the book follows the previous editions but there are some new sections, such as an additional one on colic and more detail on the care of the premature infant. The book is easily read and easy to use for reference, and would be particularly useful for the nursing student and medical student as well as for public health nurses and social workers who have to do with the care of small children.

REFRESHER COURSE FOR PRACTITIONERS. Edited by P. K. Guha, Editor of the Journal of the Indian Medical Association. 364 pp. Illust. Sri Gouranga Press Limited, Calcutta, 1955.

The subjects discussed in this refresher course for general practitioners reflect the different emphasis in the practice of medicine in India and Canada. Thus the first four articles in the book deal with malaria, kerato-malaria and diphtheria, and later contributions deal with amoebiasis, cholera and smallpox. On the other hand, a similar book prepared on this continent would be certain to contain contributions on dermatology and psychiatry—both absentees from the present work. Anyone going to work in Asia would find this little book helpful; for others it would have limited use.

LAW AND THE PRACTICE OF MEDICINE. K. G. Gray, Lecturer in Medical Jurisprudence and Forensic Psychiatry at the University of Toronto. 133 pp. The Ryerson Press, Toronto, 1955. \$3.25.

Dr. Gray has now enlarged and revised his little book on the relation of the law to medicine in Canada. For those not familiar with the first edition, which appeared in 1947, it may be said that this is not a formal text in forensic medicine, but a clearly written synopsis of the field with many references for further reading by both physicians and lawyers. The new edition includes much new material on psychiatry and the law. The practitioner or hospital administrator would be well advised to have this on his shelves as a guide in medico-legal aspects of his profession.

(Continued on page 862)

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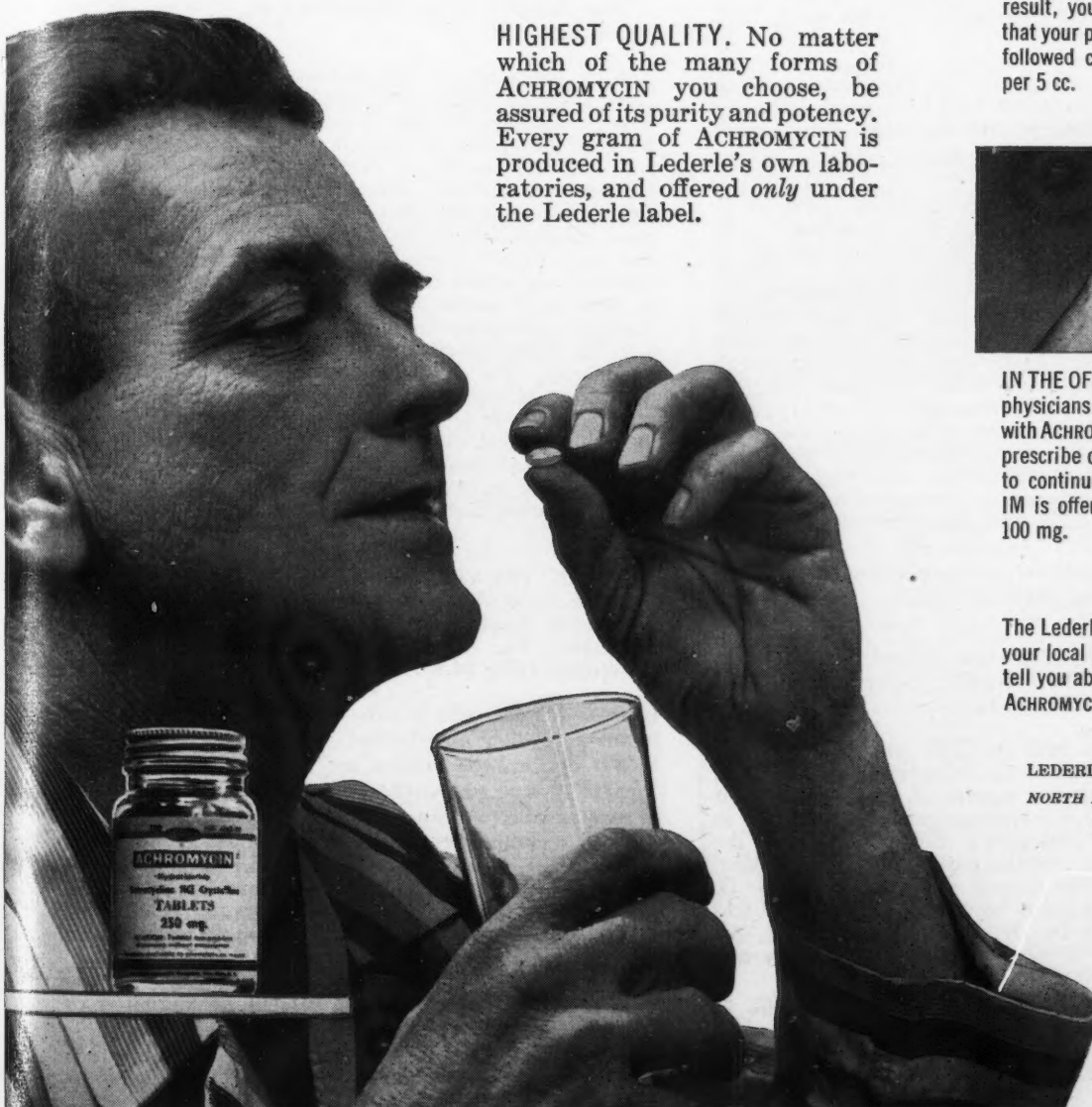
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THE BODY FLUIDS. J. R. Elkington, Associate Professor of Medicine, University of Pennsylvania, and T. S. Danowski, Renziehausen Professor of Research Medicine, University of Pittsburgh. 626 pp. Illust. Williams & Wilkins Company, Baltimore; Burns and MacEachern, Toronto, 1955. \$10.00.

Disturbances of body fluids and electrolytes are being more and more recognized as of fundamental importance in the understanding and treatment of disease processes. This book is intended to summarize our knowledge of this field, particularly from the viewpoint of these investigators, who have contributed greatly to this type of study. The fundamentals of body fluid dynamics are summarized. This is followed by an interesting chapter on comparative biochemistry. Subsequent chapters are devoted to factors which maintain the normal state, to the effects of excessive and of inadequate amounts of fluid and electrolytes and their treatment, and acid-base balance and its control. The third part discusses the fluid and electrolyte disturbances in surgical patients and in various disease conditions such as renal and cardiac failure, cirrhosis, diabetes, and adrenal dysfunctions. The final section takes up the therapeutic applications in a way which will be of great value to the practising physician. This volume contains a great deal of useful information not easily available elsewhere and it can be highly recommended.

THE AMERICAN DRUG INDEX. C. O. Wilson, Professor of Pharmaceutical Chemistry, University of Texas, and T. E. Jones, Instructor in Pharmaceutical Chemistry, University of Colorado. 576 pp. J. B. Lippincott Company, Philadelphia and Montreal, 1956. \$5.00.

With the growing complexity of the pharmaceutical industry, a reliable guide has long been needed through the forests of proprietary and non-proprietary names. *The American Drug Index* is a really valuable contribution in this respect, and will certainly be widely used by all those concerned with drugs.

It lists alphabetically, with a very adequate cross-reference system, both proprietary and non-proprietary names of drugs, together with the chemical formula, the name of the manufacturer, and the mode of presentation and of administration, dosage and uses. It goes further even than this, for it is possible to find the names of compound preparations by looking them up under the name of one constituent. Some intelligent grouping has also been done. For example, all the vitamin combinations are classified by composition and their brand names given. Choose the vitamins you want your patient to have and the dose; you can then find the name of the brand preparation corresponding—it should not be difficult for there are nearly 50 pages of such preparations listed.

This is a book which will never be allowed to gather dust on the practising physician's shelf.

JAMES PARKINSON 1755-1824. Edited by M. Critchley. 268 pp. Illust. The Macmillan Company of Canada Limited, Toronto, 1955. \$2.50.

James Parkinson was born in 1755 and this work has been brought out to mark the bicentenary of his birth. The core of the book is a reprint of Parkinson's report on the disease called the shaking palsy, now known as paralysis agitans or Parkinson's disease. To bring the book to a respectable size the editor has added a short, sensible preface, a pathological appraisal by Dr. J. G. Greenwood, a clinical essay by Sir Francis Walshe and a biographical sketch by Dr. W. H. McMenemey. Although all parts have been well done, the biography will probably appeal to the largest number of readers.

Parkinson was a Londoner who lived all his life in Shoreditch. He seems to have been a surgeon apothecary

rather than a physician or a surgeon, for he carried on a general practice, as did his father and his son. His early life covered the days of the American and French Revolutions, a period of much agitation for governmental reform in England. This agitation was carried on by societies or conferences which bore innocuous names but resorted to activities that in time of war would be looked on as subversive. These conferences issued anonymous pamphlets or manifestos to further the cause they advocated. The author of several of these publications was Parkinson, but he was never formally charged with the authorship although he did not always remain free of suspicion. As he grew older he lost interest in these publications—he may have found in them too much danger—and gave himself to the claims of his practice or to the investigation of physical phenomena free from any taint of treason.

Among Parkinson's avocations was geology. In this he became a competent amateur and was the first President of the Royal Geological Society. He had an interest also in fossils, in chemistry and in electricity. Several books on household medicine came out under his name, but apparently these did not become popular.

His fame rests on one relatively short publication describing a disease which has been given his name. Despite recurring lamentations about the evils of eponymous nomenclature his name is likely to remain in medical textbooks. Its presence there will cause less irritation than that of some who lacked something of his courage, his honesty and his modesty.

LES CAHIERS DE L'HOTEL-DIEU DE QUEBEC
(The Records of the Hôtel-Dieu de Québec). Vol. 9. 398 pp.

This is the ninth annual volume of reports from the Hôtel-Dieu de Québec and begins with an expression of good wishes to the new Dean of Medicine, Professor Jean-Baptiste Jobin. It also contains a touching obituary notice of the late Dean, Professor Charles Vézina. The greater part of the volume is as usual composed of articles from all branches of medicine, most of which have appeared either in this journal or in one of the two main French journals. Nevertheless there are a few contributions which have not previously been published. In surgery it is interesting to notice the emphasis on thoracic operations. In medicine there are communications on hypoglycaemic fatigue and on hydrocortisone in rheumatism. The dermatological section includes a 10-year study of syphilis in Québec. There are some interesting studies from the Department of Anaesthesia and the other special departments. Most of the articles are in French, but there are a few in English and one in Spanish. The printing and presentation of this volume reach the usual high standard.

MODERN TREATMENT YEAR BOOK 1956. Edited by Sir Cecil Wakeley, Senior Surgeon, King's College Hospital, London. 344 pp. Illust. The Medical Press, London; The Macmillan Company of Canada Ltd., Toronto, 1956. \$4.25.

Here is a book which can be recommended to practitioners without hesitation. Written by experienced British doctors, the articles are brief, each covering an average of nine pages; the print is easy to read. For the most part the writing is lucid, informative, devoid of verbose technicalities and unnecessary quotations from other authors. Much more than treatment is discussed, for in many instances there are useful reviews of the important diagnostic features of the conditions considered. The range of topics is as broad as general practice—all the way from biliary obstruction to worms! One good way of "keeping up" would be to read carefully and then save for reference each volume of the *Modern Treatment Year Book*.

Books Received

Books are acknowledged as received, but in some cases reviews will also be made in later issues.

The Cellular Basis of Wound Repair. M. Allgower, Privat-docent, Department of Surgery, University of Basle, Switzerland. 125 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1956. \$7.25.

The Non-venereal Diseases of the Genitals. Etiology, Differential Diagnosis and Therapy. F. T. Callomon and J. F. Wilson, Assistant Professor, Dermatology and Syphilology, Jefferson Medical College, Philadelphia, Pa. 382 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1956. \$13.75.

Atlas of Bronchial Lesions in Pulmonary Tuberculosis. C. Dijkstra, Medical Superintendent of the Sanatorium "De Klokenberg", Breda, The Netherlands. 128 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1955. \$13.25.

Experiencing the Patient's Day. R. W. Hyde, in collaboration with the attendants of Boston Psychopathic Hospital. 214 pp. Illust. Putnam & Sons, New York. \$2.20.

Malpractice Liability of Doctors and Hospitals. W. C. J. Meredith, Dean of Faculty of Law, McGill University, Montreal. 300 pp. The Carswell Company Ltd., Toronto, 1956. \$7.75.

The Truth about Cancer. Charles S. Cameron, Medical and Scientific Director, American Cancer Society. 268 pp. Illust. Prentice-Hall, Inc., Englewood Cliffs, New Jersey, 1956. \$4.95.

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Preventive Medicine in World War II, Volume III, Personal Health Measures and Immunization. J. B. Coates, Jr., E. C. Hoff et al. 394 pp. Illust. Office of the Surgeon General, Department of the Army, Washington, D.C., 1955. \$3.25.

Gullian's Theory and Practice of Nursing. 7th ed. Revised by Marion E. Gould. 243 pp. Illust. H. K. Lewis & Co., Ltd., London, 1956. 18s.

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Interpretation of Schizophrenia. S. Arieti, Clinical Associate Professor of Psychiatry, State University of New York, New York City. 522 pp. Illust. Robert Brunner, New York, 1955. \$6.75.

Colour Atlas of Oral Pathology. Prepared under the auspices of the U.S. Naval School of the National Naval Medical Center, Bethesda, Md. 188 pp. Illust. J. B. Lippincott Company, Philadelphia and Montreal, 1956. \$12.00.

Clinical Laboratory Diagnosis. 5th ed., revised. S. A. Levinson, Director of Laboratories, University of Illinois Research and Educational Hospitals, Chicago, Ill. and R. P. MacFate, Chief, Division of Laboratories, Board of Health, City of Chicago, Ill. 1246 pp. Illust. Lea & Febiger, Philadelphia; The Macmillan Company of Canada, Ltd., Toronto, 1956. \$12.50.

Skin Surgery. E. Epstein, Assistant Clinical Professor of Medicine (Dermatology), Stanford University Medical School, Stanford, California. 228 pp. Illust. Lea & Febiger, Philadelphia; The Macmillan Company of Canada Ltd., Toronto, 1956. \$7.50.

Strabismus, Diagnosis and Treatment. B. Cushman, Associate Professor of Ophthalmology, Northwestern University Medical School, Chicago, Ill. 208 pp. Illust. Lea & Febiger, Philadelphia; The Macmillan Company of Canada, Ltd., Toronto, 1956. \$6.00.

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(Continued on page 34)

MEDICAL NEWS in brief

(Continued from page 836)

PAROTID ANATOMY

For some reason the anatomy of the parotid gland has been comparatively neglected, and descriptions given in standard texts are not by any means accurate. Davis and his colleagues from Chicago (*Surg., Gynec. & Obstet.*, 102: 385, 1956) have recently published a very detailed study of the facial nerve and the parotid gland, based upon the dissection of 350 specimens. They confirm the statement of former authors, particularly Hamilton Bailey, that the parotid gland contains a superficial and a deep lobe with the main facial trunk lying between them and dividing into temporofacial and cervicofacial portions. They classify the types of facial nerve pattern into six distinct varieties. The ductules contributing to the main parotid duct arose from the superficial lobe or from both lobes in 75% of specimens examined. The transverse facial artery and external carotid artery are relatively fixed in relationship to the gland, and so are the veins. The styloid process is a snare and a delusion as a landmark, for in one-third of cases it was absent and in many others it was non-palpable and therefore of limited usefulness as a surgical guide.

Various surgeons have described techniques by which the facial nerve can be partially or wholly preserved during parotidectomy. Davis and his colleagues agree that successful excision should be possible whether the dissection be begun anteriorly or posteriorly, or whether the cervical branch of the facial or the posterior facial vein be used as a landmark to develop the natural cleavage plane.

HEALTH IN JAPAN

Dr. J. E. F. Hastings, the J. G. FitzGerald Fellow of the School of Hygiene, University of Toronto, has recently completed an interesting and instructive report* on his visit to Japan during the summer of 1955. The report covers a wide range of interests in preventive medicine.

What emerges from the report is the astounding progress the Japan-

ese people have made in regard to public health, in spite of terrific pressure of population and defeat in the last war. The population of Japan is now greater than 89,000,000, and it is increasing at a rate of about 1,000,000 each year. The crude birth rate has dropped dramatically in the last few years from a postwar high point of 34.3 per

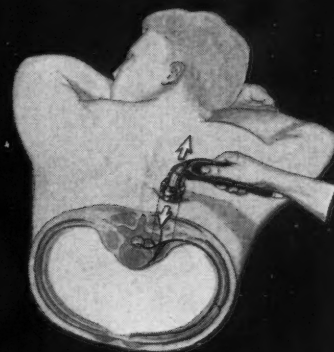
1,000 population to 20.0 per 1,000 population in 1954. This drop is ascribed to rising age at marriage, the spread of knowledge about contraception and legalized abortion. The birth rate in Canada was 28.7 per 1,000 population in 1954. The crude death rate has declined

(Continued on page 46)

Ultrasonic Therapy of Nerve Roots For Relief of Joint and Muscle Pain



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1. Behrend, H. J., and Weiss, J.: *Amer. J. Phys. Med.* 33:54 (Feb.) 1954.
2. Kobak, D.: *Amer. J. Phys. Med.* 33:21 (Feb.) 1954.
3. Jones, A. C.: *Amer. J. Phys. Med.* 33:46 (Feb.) 1954.
4. Behrend, H. J.: *New York St. J. M.* 53:403 (Feb. 15) 1953.
5. Lehmann, J. F., et al.: *Arch. Phys. Med. & Rehab.* 35:627 (Oct.) 1954.
6. Schwartz, F. F.: *Southern Med. J.* 47:854 (Sept.) 1954.

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*Hastings, J. E. F.: A Report on Medical and Health Visits in Japan, School of Hygiene, University of Toronto, 1956.

MEDICAL NEWS in brief

(Continued from page 45)

since the war, and in 1954 was 8.2 per 1,000 population, which is the same as the Canadian figure for that year. The infant death rate was 44.7 per 1,000 live births and the maternal death rate 1.8 per 1,000 live births in 1954. Life expectancy at birth is now 63.4 years for males and 67.7 years for females. In Canada the infant death rate was 35.0 per 1,000 live births

and the maternal death rate 0.8 per 1,000 live births. In 1951 life expectancy was 66.4 years for males and 70.9 years for females.

UNTREATED SYPHILIS

The late Professor Cæsar Boeck of Norway was so disappointed in his day with the treatment of syphilis that he decided to deal with a large series of cases without any drug treatment whatsoever.

His successor in Oslo, Professor Bruusgaard, continued this policy so that there now exists after the lapse of many years a number of patients who in former days had syphilis which was entirely untreated. Gjestland of Oslo (*Acta dermat.-venereol.*, 35; suppl. 34, 1955) has now investigated the fate of as many of these people as he could follow up. He finds that at least a quarter of them had a second attack of secondary syphilis, although this did not affect the further development of the disease. One in six had a benign tertiary syphilis. In 6.5% of subjects a neurosyphilis developed and in one in ten cardiovascular syphilis developed. In both these groups the incidence in males was considerably higher than in females. Neurosyphilis was the cause of death in about two-thirds of people contracting this complication, and cardiovascular syphilis killed about three-quarters of the people in whom it appeared.

Looking at the general picture, it is seen that syphilis caused the death of about one person in ten out of this series, and was more malignant in men (15%) than in women (8.3%). Syphilis did not affect, so far as can be seen, the ultimate fate of 72% of persons, so that it may be concluded that a large number of cases in this era were benign. It should not, however, be forgotten that syphilis in various epochs has apparently varied greatly in severity. It should also be remembered that, although these would not appear in statistics, there must have been a number of subjects in whom syphilis was a contributing cause of death.

AWARD TO
DR. PAPANICOLAOU

Dr. George N. Papanicolaou, Professor Emeritus of Clinical Anatomy, Cornell University Medical College, has been awarded the \$5,000 Passano Foundation Award for 1956. On June 13, during the week of the American Medical Association convention in Chicago, a reception and dinner will be held at Palmer House, at which the award will be made formally. The award to Dr. Papanicolaou is being made for his fundamental researches in exfoliative cytology, now widely applied

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THE COST OF DRUGS

Pharmaceutical manufacturers in Canada have embarked on a public relations project to explain the reason for the cost of drugs. One feature of the project is the distribution of an amusing but very informative booklet entitled "I hate to buy drugs, but". Copies of this booklet have been distributed to physicians and pharmacists across Canada; extra copies are available to physicians.

NEW SKIN ANTISEPTIC

From the University of Alberta, Myers and his colleagues (*Canad. J. Microbiol.*, 2: 87, 1956) report *in vivo* tests of a new skin antiseptic. They tested the tincture and an aqueous solution containing 0.5% of 1,6-DI-4'-chlorophenyldiguanidohexane by taking skin biopsies from various operative sites before and after a measured time of exposure to the antiseptic. They neutralized the antiseptic at the end of the exposure time and tested bactericidal activity by a standardized series of culture procedures. The aqueous solution and the tincture have marked skin disinfectant properties against a wide range of micro-organisms including *Micrococcus pyogenes aureus* and *albus*, diphtheroids, *Streptococcus viridans* and *B. coli*. Exposure to the aqueous solution for three minutes resulted in no growth in 76% of specimens tested, while exposure for four minutes stopped growth in 95%.

HEMISPHERECTOMY IN TREATMENT OF HEMIPLEGIA

Dr. Ferey of Rennes, France, (*Presse méd.*, 64: 81, 1956) describes his experience with the operation of cerebral hemispherectomy

in the treatment of hemiplegia and certain other encephalopathies in childhood. He has operated upon 10 cases within the last three years with very good results. In most cases there was a hemiplegia due to birth injury, together with epilepsy, character disturbances and mental retardation. In three cases the hemiplegia had followed an encephalitis of unknown origin, and in one case a cranial fracture in infancy was responsible. Dr. Ferey considers that hemispherectomy should be carried out only on patients in whom careful examination, including arteriography, has shown that one cerebral hemisphere is completely healthy. The indications for opera-

tion include major epilepsy, severe disturbances of personality, major mental deficiency and hemiplegia. The most constant result was the complete disappearance of hemiplegia in eight of the ten; disturbances of character were also ameliorated and the mental condition improved.

X-RAY CINE-ANGIO-CARDIOGRAPHIC AND KYMOGRAPHIC STUDY OF THE AURICULAR APPENDAGES

An article by E. Giacobini and C. Simonetti, of interest to the

(Continued on page 48)



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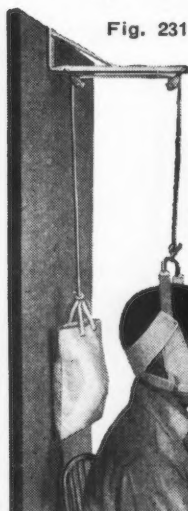


Fig. 231

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MEDICAL NEWS in brief

(Continued from page 47)

cardiologist, radiologist and anyone especially interested in cardiac anatomy or physiology, appears in *Camera Radiologica* (Dagra Ltd., Amsterdam, January 1956), presenting a careful study of the morphology and variations of the auricular appendages in the normal and in a variety of disease states, as demonstrated by cinematographic records during angiocardiology and kymography. The illustrations are very numerous and of a very high quality. This is a free publication and, judging by this issue, warrants the attention of radiologists in general and of physicians who may be interested in specific subjects which will form the basis of future publications.

TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS

Pilkington and his colleagues from London, England (*J. Lab. & Clin. Med.*, 47: 652, 1956), have examined the action of six antibiotics singly and in combination on enterococci isolated from cases of subacute bacterial endocarditis. After studying the effect of the antibiotics on 18 strains of enterococci, they draw certain important therapeutic conclusions. They point out that subacute bacterial endocarditis is a disease in which the organism must be killed by the antibiotic and not just inhibited. It is also probable that blood concentrations greater than the "minimum bactericidal level" are needed to enable the drug to diffuse into the lesions and maintain a local lethal activity. The choice of antibiotic is therefore much more limited than in other infections, and customary tests for antibiotic sensitivity may be misleading as well as inadequate. Pilkington and his colleagues confirm that for penicillin and streptomycin inhibitory concentrations are very close to bactericidal ones, but for newer antibiotics these two levels are often far apart, so that choosing a drug on the basis of an inhibition test may lead to failure of therapy. The synergism of penicillin and streptomycin is recognized, but the clinical significance of antagonism has not yet been clarified. Combining a bactericidal

antibiotic with a bacteriostatic one might lead to antagonism. The present authors' tests tend to confirm this for penicillin but not streptomycin.

CHLORPROMAZINE IN ANÆSTHESIA

Albert and his colleagues from Washington, D.C. (*Current Res. in Anesth. & Analg.*, 35: 101, 1956) have studied the use of chlorpromazine in anaesthesia and come to the following conclusions. Chlorpromazine given intravenously during anaesthesia in doses of 1 mg. per kg. bodyweight in dilute solution over a period of 15 minutes decreases myocardial irritability and blocks adrenaline action. As premedication it will potentiate the action of depressant anaesthetic drugs, will reduce vomiting after anaesthesia and will control agitation. Delirium tremens has also been controlled effectively. Hypotension is a serious complication and patients given chlorpromazine should be watched carefully for this occurrence.

SENSITIVITY TO ALCOHOL IN HODGKIN'S DISEASE

Attention is again drawn to the occurrence of pain immediately after drinking alcohol in patients with Hodgkin's disease. This phenomenon was first mentioned in 1950 in the U.S.A. and has later been commented on by Danish and English observers. In the most recent report, four patients with this unusual symptom were seen at the Mayo Clinic (*J. A. M. A.*, 160: 1274, 1956). The pain may be accompanied by intense generalized pleuritis and is described as acute, distressing, burning or terrible. It arises either during consumption of an alcoholic beverage or soon after and persists for from 10 minutes to an hour. It may be an indication for further search for Hodgkin's disease or may prove of value in detecting a recurrence of treated Hodgkin's disease.

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and debilitated patients who in a former era would have been considered inoperable. Because of this, he encounters a greater incidence of episodes of adrenal-cortical insufficiency at operation or immediately after. At the Memorial Center for Cancer and Allied Diseases, Cornell University Medical College, Howland and his colleagues have tried the effect of intravenous injection of hydrocortisone (100 mg. in 500 c.c. of glucose in water) to counteract signs of adrenal-cortical insufficiency at operation. These signs include persistent hypotension with failure to respond to adequate blood replacement or to vasoconstrictors, respiratory depression, and a prolonged reaction time after anaesthesia. In seven cases described in their report (*J. A. M. A.*, 160: 1271, 1956) the intravenous administration of hydrocortisone produced a rapid response.

PVT EXCRETION IN NEPHRITIS AND TOXÆMIA OF PREGNANCY

Herold of Düsseldorf (*Deutsche med. Wchnschr.*, 81: 402, 1956) suggests the use of polyvinylpyrrolidone (PVT), a chain polymer of high molecular weight, as a test for differentiation of different forms of toxæmia of pregnancy. In normal pregnant women, urinary excretion of PVT is higher than in non-pregnant ones. In toxæmia of pregnancy, it is diminished and delayed (30% in six hours, compared to a normal of 50%). To study the relation between pre-existing chronic nephritis and toxæmia of pregnancy, PVT excretion was studied in 28 patients with chronic nephritis. They received an intravenous injection of 800 mg. of PVT in 20 c.c. of saline. The delay in excretion was even more marked than in toxæmia of pregnancy. It was noted that in what the author calls "essential" toxæmia, normal excretion values were quickly restored after delivery, whereas when toxæmia was an overlay of nephritis, the excretion rate continued to be low, as in chronic nephritis. Herold suggests that this test may be used for differentiating the two forms of toxæmia of pregnancy, and as a basis for prognosis.

MITRAL COMMIS- SUROTOMY, THE INTERNIST AND THE G.P.

In the present status of mitral commissurotomy the chief responsibility of the internist and the general practitioner is to recognize cases of mitral stenosis in time, to watch their course regularly and carefully and lead them to the cardiac surgeon in an early stage and not when right heart failure has set in. The guide for operation is not too soon and not too late.—Halhuber, M. J.: *Wien. med. Wchnschr.*, 106: 273, 1956.

ORAL HYDROCORTISONE IN PNEUMOCOCCAL PNEUMONIA

It has been shown that the beginning of bacterial or viral infection in animals receiving cortisone or ACTH is followed by unusually rapid progression of infection with the outcome in favour of the parasite. On the other hand, where steroids have been administered after infection has become established or where antibiotics are being currently given, the results are less well documented. In view of the belief that such steroids may facilitate recovery in severe human infection by suppressing "toxæmia", a study was made at the Johns Hopkins Hospital between October 1, 1954 and May 31, 1955 of the effects of oral hydrocortisone upon the course of pneumococcal pneumonia. All the patients submitted with pneumococcal pneumonia without bacterial complications during this period were included in the study, being assigned to one of two groups. The first group of 52 patients received the usual treatment with aqueous potassium penicillin G intramuscularly in a dose of 300,000 units every 12 hours for seven days or until the patient had been afebrile for 48 hours. In addition they were given hydrocortisone by mouth to a total of 560 mg. in five days, namely, 80 mg. on admission, 60 mg. every six hours for three doses, 40 mg. every six hours for four doses, 20 mg. every six hours for four doses, 10 mg. every six hours for four doses and 10 mg. every 12 hours for two doses. There were two deaths in the series, one from each group. There were no

(Continued on page 50)

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MEDICAL NEWS in brief

(Continued from page 49)

suppurative complications in either group and the common complications of steroid therapy were not observed. One patient had to be taken off hydrocortisone because of the development of an alarming hypothermia. In general it appears that giving hydrocortisone in the dosage mentioned above to patients already receiving penicillin for pneumonia improves their symptoms more rapidly and makes them more comfortable during the acute phase of the disease. It does not however shorten the time required for complete restoration to normal. The most striking feature was the more rapid disappearance of fever in patients given hydrocortisone. It is concluded that a further cautious exploration of the value of such steroids as adjuvants to specific therapy in pneumococcal pneumonia is justified.—Wagner, H. N. *et al.*: *Bull. Johns Hopkins Hosp.*, 98: 197, 1956.

PAN-AMERICAN CONGRESS OF OPHTHALMOLOGY

The Pan-American Association of Ophthalmology announces that preparations are well in hand for its Fourth Interim Congress in New York on April 7-10, 1957. It will be held at the Hotel Statler and those intending to participate should make reservations direct with the hotel. There will be three official subjects for discussion by invited speakers—diseases of the ocular fundus; ophthalmic surgery; therapeutics and present-day ophthalmology. Those wishing to present papers are invited to communicate with Dr. John N. McLean, The New York Hospital, 525 East 68 Street, New York 21, N.Y.

SPECIALISTS IN CANADA*

The Department of National Health and Welfare has recently published statistical information on the number and distribution of various types of medical specialists in Canada, as a supplement to their 1954 survey of physicians. At June 1954 there were 6,246 specialists, of whom 4,550 were in private practice. The statistics show considerable variation in distribution of specialists. The highest proportions of total physicians doing specialist work are in the provinces of New Brunswick, Quebec, Manitoba and British Columbia. In Quebec, the number of specialists in private practice greatly exceeds the number of general practitioners, whereas in most other provinces general practitioners are much more numerous than specialists. Of those in private specialist practice, no less than 74% are certificated by the Royal College of Physicians and Surgeons of Canada; there is a much lower proportion for those not in private practice, because so many of the latter are in fields such as industrial medicine and various branches of public health for which the Royal College does not certify. Almost 30% of specialists were in general surgery or internal medicine; this figure is fairly constant among most of the provinces. A provincial

*From supplement to "Survey of Physicians in Canada", June 1954, Memorandum No. 2, General Series, Research and Statistics Division, Department of National Health and Welfare, Ottawa, October 1955.

breakdown of certificated and non-certificated specialists shows that Ontario and British Columbia had relatively high proportions of certificated persons, whereas Quebec and Manitoba had relatively low figures. The growth of specialism in Canada as a whole is reflected in the fact that the number of specialists increased by nearly 32% between 1949 and 1954, while the total number of physicians increased only by 15%. The increase in specialists was heavily weighted with non-certificated individuals. It is notable that 413 physicians who hold specialist certificates are not specializing; about half of these physicians are in Ontario.

OPERATIONS FOR DUODENAL ULCER

The Billroth I operation is now regarded by many surgeons as the operation of choice in cases of gastric ulcer. Its suitability for treatment of duodenal ulcer is, however, not on such firm ground. Goligher and his colleagues from Leeds, England (*Lancet*, 1: 220, 1956), are of the opinion that the Billroth I operation is much inferior to the Polya operation for the treatment of duodenal ulcer. They base this belief on a follow-up study of all cases of duodenal ulcer operated on during the years 1948-1954. Approximately half of these (312 patients) were treated by Billroth I and half by Polya resection. There were 12 deaths in the postoperative period, all due to leakage and peritonitis from a sutured duodenal stump or anastomosis. Altogether 132 patients treated by the Billroth I and 138 by the Polya gastrectomy were followed up and study was made of the incidence and site of recurrent ulceration, the frequency of symptoms not due to ulceration, and the functional state of the patient, determined by his fitness for work and his enjoyment of life. As regards recurrent ulceration, the difference between the two series is striking. The recurrence rate after three years was 17.5% after Billroth I operations and only 1.9% after Polya operations. There was a definite tendency for recurrent ulceration on the lesser curve of the stomach after Billroth I resec-

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MEDICAL NEWS in brief

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tion. The patient's functional state was on the whole somewhat better after a Polya operation than after a Billroth I.

SWELLING OF THE SCROTUM IN INFANTS AND CHILDREN

Out of a series of 158 cases of swelling of the scrotum in male infants and children, collected in the Department of Pædiatric Surgery of a Stockholm hospital, 12 proved to be cases of non-specific epididymitis. It is the practice of the author, Dr. Qvist, (*Acta chir. scandinav.*, 110: 417, 1956) to operate upon cases of childhood swelling of the scrotum in which diagnosis presents difficulty. If an incarcerated hernia or torsion of the testis is found, operation is then the appropriate treatment. If the condition is due to an acute epididymitis, the diagnosis will be made clear at operation and this is often the only way of making the diagnosis. The prognosis is favourable.

CANCER OF THE CERVIX

Dr. Guillemin of Nancy reports a study of gynaecological conditions in 11 religious orders in eastern France. His series includes 1,725 nuns whom he had seen over a period of 30 years. During these three decades he had operated upon 687 of them, and now analyzes the gynaecological conditions for which operation was necessary. As in the series reported by Gagnon on Canadian nuns, Guillemin finds a particularly low incidence of carcinoma of the cervix. The commonest cause for gynaecological operation was fibroids, followed in order by carcinoma of the breast (counted as a gynaecological condition in France), ovarian cyst, breast adenoma and cyst, cervical polyp, and (low on the list) uterine cancer and bladder cancer. In the present series there were three cases of cancer of the body of the uterus to four cancers of the cervix; this is an unusual proportion, for Meigs considers that in an average ordinary population there are six cancers of the

cervix to every cancer of the body of the uterus.

These figures confirm the fairly well-established fact that virgins are immune from uterine cancer. Since they are subject to hormonal changes, as are other women, it is concluded that the absence of chronic inflammation is the protective factor.—*Bull. Acad. nat. méd.*, 140: 105, 1956.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

Applications for certification (American Board of Obstetrics

and Gynecology) for the 1957 Part I examinations are now being accepted. Candidates are urged to make such application at the earliest possible date (deadline October 1, 1956). All candidates for admission to the examinations are required to submit with their application a plain typewritten list of all patients admitted to the hospitals where they practise, for the year preceding their application or the year prior to their request for reopening of their application.

Application for re-examination, as well as requests for resubmission

(Continued on page 56)

Rx INFORMATION

INDICATIONS: Menopause, prostatic carcinoma, postpartum breast engorgement.

COMPOSITION: Each capsule, or 1 cc., contains 12 mg. of TACE (Chlorotrianisene).

SAFETY: TACE produces a minimal incidence of withdrawal bleeding so commonly observed following estrogen therapy of the menopause. In both sexes, TACE is generally well tolerated, thus minimizing such side effects as nausea, vomiting and fluid retention.

DOSAGE: For relief of menopausal symptoms, 2 TACE Capsules, or 2 cc. TACE Oral Drops (in cold water), daily for thirty days, is generally a course of therapy. In severe cases when symptoms recur, additional short courses of TACE may be required. For postpartum breast engorgement, 4 TACE Capsules daily for seven days. For palliative control of prostatic carcinoma, 1 or 2 TACE Capsules daily.

SUPPLIED: In bottles of 60 and 300 capsules; in 30 cc. bottles with calibrated dropper. One bottle of capsules or 2 bottles of oral drops usually suffice for a course of therapy.

References: 1. Greenblatt, R. S., and Brown, N. H., *Am. J. Obst. & Gyn.* 63:1361, June, 1952.
2. Ausman, D. C., *Wisconsin M. J.* 53:122, 1954.
3. Woodhall, R. B., *Obst. & Gyn.* 3:201, 1954.
4. Ivory, H. S., *J. Med. Soc. N. J.* (In press).

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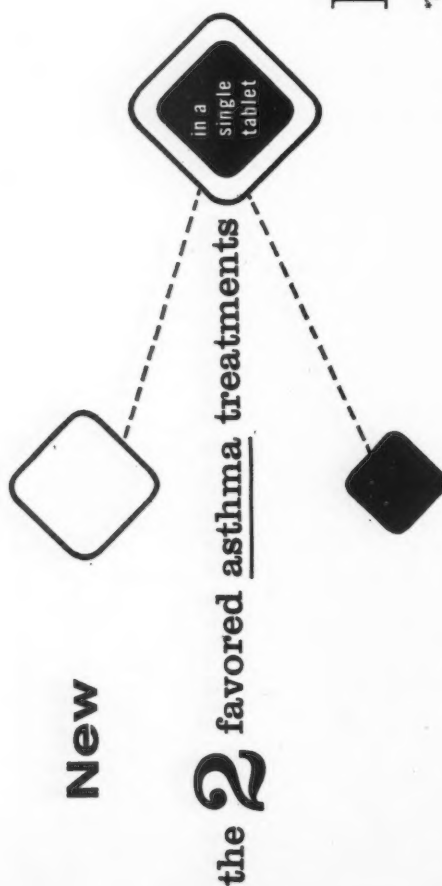
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MEDICAL NEWS in brief

(Continued from page 55)

of case abstracts, must be made to the Secretary before October 1, 1956. Current bulletins outlining present requirements may be obtained by writing to the Secretary's office, 2105 Adelbert Road, Cleveland 6, Ohio.

DON'T FORGET THE GOUT

The case is recorded by two French authors (*Presse méd.*, 64: 613, 1956) of a gouty old gentleman of 64 who had suffered from manifestations of this disease since the age of 28 but without ever having the correct diagnosis made. He had suffered attacks of pain in the large joints (knee, wrist, ankle) and had been treated at times for acute rheumatism, infective arthritis and other conditions. He had also had an attack of renal colic. It was noteworthy that during the war when his diet was restricted he suffered no pain. There was a past history of excessive eating and drinking, but for many years before the diagnosis was finally made he had been a temperate and slim man. Never once was the great toe involved in these attacks, and the diagnosis was only confirmed eventually by his being given colchicine, which promptly abolished his current attack. The authors also recall the case of a man who had had rheumatism for 41 years before a typical attack of pain in the great toe was observed. They warn that only 41% show an affection of the great toe, and that the commonest reason for not diagnosing gout is not thinking of it.

TREPONEMA PALLIDUM IMMOBILIZATION TEST

Two papers in the *Journal of the American Medical Association* for April 21, 1956 (p. 1392 and 1394) discuss recent studies of the Treponema pallidum immobilization test as a diagnostic aid for syphilis. The first article by Ledbetter reports the results of study of over 4,000 sera. It was found that the test was helpful in eliminating both false-positive and false-negative results given by older serological tests. The second paper by Miller and his colleagues discusses the use of the Treponema pallidum immobilization test in spinal fluid.

The authors examined 376 specimens and conclude that levels of immobilizing antibody are usually significantly lower in the spinal fluid than in the blood. A negative result in spinal fluid need not necessarily exclude the diagnosis of neurosyphilis (there were 14 such results out of 100 proven cases), but a positive immobilization test indicates definite evidence of neurosyphilis. Tests should be carried out on fresh specimens, since antibody levels tend to fall with storage.

SAFEGUARDS IN ABDOMINAL SURGERY IN THE AGED

Experience with 198 patients aged 70 or more undergoing major abdominal surgery leads to the enunciation by Gilchrist and de Peyster of Chicago (*J. A. M. A.*, 160: 1375, 1956) of seven safeguards which in their hands have lowered mortality and morbidity in elderly patients subjected to major surgery. The safeguards are: (1) use of complementary local subcostal block anaesthesia with peritoneal infiltration under direct vision on opening and closing the abdomen; (2) maintenance of normal blood volume by small daily transfusions (250 ml.), particularly where chronic infection is present or where prolonged parenteral nutrition is required; (3) institution of prophylactic anticoagulant therapy begun on the second or third postoperative day in patients with a previous history of thromboembolism or in those hypotensive patients subjected to extensive or prolonged surgery; (4) maintenance of constant infusion of glucose or electrolyte solution (250 to 300 ml. per hour) during operation to combat haemoconcentration, care being taken to avoid excess fluid and electrolyte loading during the first two or three postoperative days; (5) prevention of cardiorespiratory and patient fatigue by the liberal use of oxygen with or without such detergents as Alevaire (mucolytic aerosol) and such bronchial dilators as isoproterenol (Isuprel) hydrochloride; (6) postoperative decompression of the alimentary tract by gastrostomy; and (7) insertion of an indwelling urinary catheter and establishment of an accurately recorded electrolyte and fluid balance chart totalized and balanced every eight hours.

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Therefore, the NEW Herisan Antibiotic Ointment (1) provides a high level antibiotic action with low dosages of Bacitracin, Tyrothricin and Neomycin due to their marked synergistic action in combination, (2) has a low toxicity rating, (3) has a low sensitizing power, (4) is effective in the presence of blood, pus, plasma, necrotic tissue and penicillinase, (5) stimulates the formation of granulation tissue, (6) ensures rapid healing and thus treatment is of shorter duration.



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- (1) Dickson, R.M.: Brit. J. Ophth. 26:529, 1942.
- (2) Collier, E.: Brit. J. Phys. Med. 6:181, 1943.
- (3) Dickson, R.M.: Brit. J. Phys. Med. 7:77, 1944.
- (4) Kuhn, H.S.: Tr. Am. Acad. Ophth. 55:431, 1951.

Thirty Years Ago . . .

From the Journal of June, 1926

(Extract from a letter from a Canadian doctor travelling in Italy):

"It was very unfortunate that Mussolini was injured after delivering his address of welcome to our Association (International Surgical). I shook hands with him five minutes before he was wounded. His address impressed me most favourably. He has a fine manly dignified presence, a pleasing voice and his manner was excellent. He is doing wonders for Italy and indeed for the world in saving Italy from Bolshevism. He has all the better Italians behind him and is carrying into effect the best Italian ideals."

Federation of Medical Women. Organization of the medical women of Canada as a national federation having affiliation with the Medical Women's International Association has been under consideration for some years past, and an informal preliminary meeting was held in Montreal in June 1923. As a result of action then taken and of an urgent request from the British Federation of Medical Women for Canadian representation at the meeting of the Medical Women's International Association in London in 1924, an organizing meeting was held in Ottawa in June 1924 during the meeting of the C.M.A.

British Columbia. Dr. J. H. MacDermot of Vancouver has been appointed to represent the B.C. Medical Association on the Board of Trustees in connection with the proposed Preventorium, to which the Rotary Club of Vancouver has given \$10,000.

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The Canadian Medical Association Journal

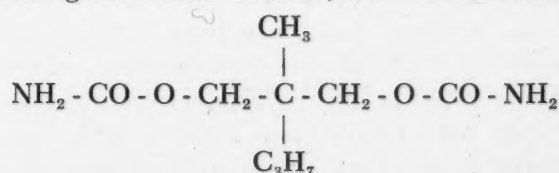
JUNE 1, 1956 • VOL. 74, NO. 11

MEPROBAMATE (EQUANIL) FOR RELIEF OF ANXIETY AND NERVOUS TENSION FROM VARIOUS CAUSES

S. E. C. TURVEY, M.D., *Vancouver, B.C.*

WHERE IS THERE A PERSON who does not hope for freedom from worry and anxiety? Since even in the ordinary vicissitudes of life many tension-producing situations arise, and under special conditions nervous strain may become intolerably severe, temporary help from medication is often desirable to render this tension less burdensome. Hence in the continued search for the perfect sedative a large series of vegetable products have been investigated, from fermented grains to the poppy seed, and finally to the root of rauwolfia, but none has approached the ideal.

One of the latest of the anxiety-relieving agents is a synthetic chemical compound, meprobamate (Equanil). Designated chemically as 2-methyl-2-n-propyl-1:3-propanediol dicarbamate, meprobamate was first synthesized by Ludwig and Piech¹ in 1951, with the formula



PHARMACOLOGY

A white crystalline powder with a bitter taste and faint odour, meprobamate is soluble in most organic solvents and relatively insoluble in water. The compound is stable in dilute acid and alkali, and therefore is not broken down by the gastrointestinal secretions. Meprobamate resembles mephensin in structure but lacks the hydroxyl groups, which are rapidly oxidized within the body with resultant transience of action.

Meprobamate is described as an interneuronal blocking agent with pronounced muscle-relaxing properties.² In animals the compound produces a reversible paralysis of voluntary muscles without significant effects on the autonomic nervous system.³ Internuncial circuits are inhibited without alteration of transmission at the myoneural junction

tion or blocking of conduction in the peripheral nerves. Large therapeutic doses produce no untoward effects on blood pressure or respiration.

In cats, multineuronal reflexes are abolished without interfering with the knee jerk. Electrical recordings from the cerebral cortex and diencephalon after intravenous injection show synchronization of activity with moderate slowing of frequency and increase of voltage. The pattern is quite different from the spindling seen after administration of barbiturates. The effects are first detectable in the region of the thalamus and caudate, and the increase in voltage is greater in these areas than in the cortex.

The fate of meprobamate in the body is unknown. The kidney excretes about 10% unchanged and an additional 10% in conjugated form. Some studies have indicated that a large portion is probably conjugated to a glucuronide or similar metabolite.

PREVIOUS TRIALS

In previous clinical trials by competent observers,⁴⁻⁷ meprobamate has been administered in 400 mg. tablets, usually in total daily doses of 4 to 8 (1.6 to 3.2 g.). In general, the compound acts as a mild relaxant, usually producing in the patient a tendency to natural sleep. In the intoxicated patient, meprobamate relaxes tension without stimulating the undesirable secondary response that commonly occurs after treatment with the barbiturates. In agitated individuals suffering from anxiety, depression and tension, a tendency to sleep is a particularly desirable effect. Additional sedation at night usually is unnecessary. For daytime control of nervous tension, 400 to 600 mg. every six hours causes generalized muscular relaxation, lessens nervousness, and reduces irritability and restlessness.

Somewhat similar observations have been reported after administration of promethazine, chlorpromazine, the rauwolfia derivatives and various other products.

In any group of neurotic patients, relief will occur in a certain percentage after use of almost any agent, provided the treatment is administered by a sympathetic physician. An even greater percentage will report benefit from a drug with action so mild or transient as merely to suggest an effect. What the physician needs is an agent that is harmless to the body economy,